

## Background Report Regarding Poul Thorsen, MD

**Tax evasion, money laundering, wire fraud, violations of dual employment regulations leading to dismissal at his research university -- all connected with stealing grant money through an elaborate scheme of falsifying invoices and forging signatures....With all these criminal irregularities, how can anyone trust the data this researcher produced? Why haven't calls for retracting his studies gone out? The details of these issues are summarized in this report, including exhibits confirming sourcing.**

**Federal Charges:** The most troubling aspect is the April 13, 2011 indictment of Poul Thorsen. The United States Attorney's Office in the Northern District of Georgia issued a public statement (Exhibit 1) announcing that a federal grand jury had indicted Poul Thorsen, (MD, PhD) 49 years old of Denmark on 13 counts of wire fraud and 9 counts of money laundering. United States Attorney Sally Quillian Yates stated that Dr. Thorsen "is alleged to have orchestrated a scheme to steal over \$1 million in CDC grant money earmarked for autism research."

*Nature* (Exhibit 2) online printed the following announcement on April 20, 2011:

**Research fraud** Prosecutors in the United States are seeking to extradite a Danish scientist researching the relationship between autism and vaccines, who, they allege, stole more than US\$1 million in research funding. Poul Thorsen was a visiting scientist at the Centers for Disease Control and Prevention (CDC) in Atlanta in the 1990s. US prosecutors say that after returning to Denmark in 2002, Thorsen submitted false invoices from the CDC to Aarhus University, which unknowingly transferred funds to his personal account. He was last week charged with 13 counts of wire fraud and 9 of money laundering .

**The Indictment:** The Criminal Indictment No. 1: 11-C R-194 United States of America v. Poul Thorsen (Exhibit 3) states that beginning around February 2004 and continuing through February 2010, that "aided and abetted by others known and unknown, did knowingly devise and intend to devise a scheme and artifice to defraud and to obtain money and property by means of materially false and fraudulent pretenses, representations, and promises and omissions of material facts, well knowing and having reason to know that said pretenses, representations and promises were and would be false and fraudulent..." The indictment provides that Thorsen submitted false invoices and created private bank accounts at the CDC Federal Credit Union to which he had monies wired to pay invoices (from a CDC laboratory using false signatures) and then used the monies (close to \$1million) to purchase a Harley Davidson motorcycle, two automobiles and a home listed as a 4 bedroom, 5 bath 2688 sq ft home at 2657 Briar Lake Road, Atlanta, Georgia 30345.

The Justice Department provides that it will seek to recover all of the property that Poul Thorsen purchased, however; the home listed in the indictment in April 2011 was foreclosed on by the lender in March 2011, removing it from Thorsen's ownership at the time of the indictment. Available data show that there was an attempt to sell the listed home for almost \$500,000, the price was dropped repeatedly and then withdrawn from market. (Exhibit 4)<sup>1</sup>

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<sup>1</sup> Conversation with realtor with access to Georgia MLS systems confirmed that Thorsen had owned the property, that it had been listed for sale in the high \$400'000s and then dropped at least 3 times in price into the \$300,000s before being removed from the market by the bank which had foreclosed on Thorsen in March 2011.

## Background Report Regarding Poul Thorsen, MD

If convicted on all counts, Poul Thorsen could face up to 260 years in prison and \$22.5 million in fines. (Exhibits 5 and 6)

**Poul Thorsen:** Thorsen stands as the lead-researcher on all CDC-funded Danish research used to counter arguments from families claiming their children suffered vaccine injuries including, among other conditions, the onset of symptoms of autism spectrum disorder.

Dr. Thorsen acted as a visiting scientist at the (CDC) Division of Birth Defects and Developmental Disabilities. He successfully promoted the idea of awarding research funds to Aarhus University in Denmark to study the relationship between autism and vaccines. He “provided input and guidance for the research to be conducted.” (Exhibit 1) It would appear that he built a strong relationship with CDC staff, and beginning in 2001 began a relationship that has underwritten his entire career. Beginning in 2001, Dr. Thorsen lists himself as affiliated with both a) the Developmental Disabilities Branch, Division of Birth Defects, Child Development, and Disability and Health, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta and b) Danish Epidemiology Sciences Centre, Aarhus University. He is further listed as the corresponding author of the paper. (Exhibit 7) A year later he removed the Aarhus University affiliation from his next publication and only listed his CDC affiliation with colleague Dr. Diana Schendel. (Exhibit 8)<sup>2</sup>

Dr. Schendel has continued to collaborate with Dr. Thorsen even after the indictment, co-authoring two articles in the second half of 2011. At the time his article was published in 2003, *Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data*, Thorsen claims an affiliation with the Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Aarhus, Denmark.

**Affect on long-term US policy making:** Dr. Thorsen claims active engagement with the American Psychiatric Association (APA) in the development of the highly controversial fifth edition of the Diagnostic and Statistical Manual (DSM-5). According to the brief bio (Exhibit 9), provided for the APA DSM-5 Working Group on January 22, 2010, Dr. Thorsen listed his current position as Adjunct Associate Professor, Department of Epidemiology and Biostatistics, School of Public Health, Drexel University, Philadelphia, PA, USA.

Thorsen claims he started his first project in 1987 while still a medical doctoral student, and that he “managed a considerable number of studies on autism, national as well as international” further claiming his research career began in 1992.

- 1996 - Began work on the Danish National Birth Cohort
- 1997-2000 - Visiting scientist, CDC

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<sup>2</sup> Ment Retard Dev Disabil Res Rev. 2002;8(1):39-45. Public health issues related to infection in pregnancy and cerebral palsy. Schendel DE, Schuchat A, Thorsen P. Source Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, USA. dcs6@cdc.gov

## Background Report Regarding Poul Thorsen, MD

- 2000-2008 - Associate Professor, Department of Epidemiology, School of Public Health, University of Aarhus, Denmark,
- 2008-2009 - Research Professor, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA,
- 1999-present - Associate, Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA.
- 1998-2005 - March of Dimes, PERI grantee
- 1999-2008 - CDC appointed principal investigator on the “Epidemiologic studies of reproductive and developmental outcome – Denmark”
- Dr. Thorsen authored or co-authored more than 90 scientific articles and book chapters.

During the period 2000-2008, the bio claims that Dr. Thorsen established the research group known as “North Atlantic Neuro-epidemiology Alliances” (NANEA) originally initiated to do research on Cerebral Palsy in 1999-2000. He provides that in January 2010, more than 30 researchers are affiliated. NANEA’s main research areas were:

- a) Autism
- b) Cerebral palsy
- c) Neuropsychological development
- d) Preterm birth
- e) Down syndrome, and
- f) Hearing loss

On the APA DSM-5 working group website it states Thorsen participated in the *Autism and Other Pervasive Developmental Disorders Conference* in February 2008. (Exhibit 10) The DSM-5 has come under fire for proposing changes to the criteria for autism spectrum disorders that would in some opinions prevent as many as 75% of higher function or Asperger’s individuals from qualifying for services.

The evidence shows Thorsen was not involved in autism research until the 2002 article on the MMR vaccine and autism. Prior to this, most of his publications focus on sexually transmitted diseases, infections during pregnancy, and neonatal research – more of a shotgun approach to vaccines and public health issues rather than a bull’s-eye topical focus that most feel makes one an expert in a field.

**Thorsen Broke Other Rules as Well:** January 2010, Aarhus University issues a formal statement (Exhibit 11) distancing itself from Poul Thorsen, confirming that the University discovered shortages of funds in the CDC grant accounts. This was reported to the Danish Agency for Science, Technology and Innovation (DASTI). DASTI conducted an internal investigation and referred the matter to the police. The letter states: *“In March 2009, Dr. Thorsen resigned his faculty position at Aarhus University. In the meantime, it has come to the attention of Aarhus University that Dr Thomsen has continued to act in such a manner as to create the impression that he still retains a connection to Aarhus University after the termination of his employment by the university. Furthermore, it has come to the attention of Aarhus University that Dr. Poul Thorsen has held full-time positions at both Emory University and Aarhus University simultaneously. Dr. Thorsen’s double Full-time employment was*

## Background Report Regarding Poul Thorsen, MD

*unauthorized by Aarhus University, and he engaged in this employment situation despite the express prohibition of Aarhus University.” (Exhibit 11)*

In addition to the criminal acts uncovered, Aarhus publicized that Thorsen violated the rules of employment for the University. This demonstrates a pattern of unethical behavior by Thorsen, one indicating that rules do not matter – that he is above the law, above university rules, and likely above ethical standards of good science.

**Tax Evasion:** Danish Journalist Ulla Denielsen reported via a blog that the Danish government sought to prosecute Poul Thorsen for tax evasion. In 2009 the prosecution charged Poul Thorsen, with gross tax evasion concerning an amount of fully 6,4 million DKK (US\$ 1.13 million). For this, the Prosecution claims Poul Thorsen must be punished with prison. As stated in the indictment, Poul Thorsen during the years 2001-2005 evaded income from fees, salary or the like for 6,430,768 DKK. Thorsen’s attorney sought to have the charges be dismissed. A hearing scheduled for March 29, 2012 dismissed the charges on technicalities based on deficits in the indictment, not because Thorsen was exonerated from the charges. (Exhibit 12&13)

**Autism Related Papers:** Thorsen’s entry into the autism research realm began in 2002 with the publication of the first Aarhus/CDC paper. In the decade since, he has co-authored 21 papers (2 in a Danish journal, likely identical to two English language publications, so in essence 19 studies.) (Exhibit 14) These publications started after he returned to Aarhus University in 2002; beginning in 2005 he claimed he was affiliated with North Atlantic Neuro-Epidemiology Alliances, Department of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark.

An article published online in April 2010 again with CDC employee Dr. Schendel lists Dr. Thorsen without any affiliation, but living in Atlanta. A May 2010 paper fails to include Thorsen’s affiliation. In a paper published in June 2011 (and published online a year before), Dr. Thorsen is listed as being employed at the Institute of Public Health at the Department of Epidemiology, University of Aarhus, Aarhus, Denmark. One of his co-authors is CDC employee Diana E. Schendel, Ph.D.

From December 2011 to February 2012 (following the US federal indictment) four papers were published as peer-reviewed literature and posted on PUBMED listing Poul Thorsen as a co-author. Each of these studies lists him as employed at the Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark. (Exhibit 14)

An inquiry to Lillebaelt Hospital, Kolding Denmark on March 20, 2012 confirmed that Poul Thorsen is indeed employed there and provided the email address [Poul.Bak.Thorsen@slb.regionsyddanmark.dk](mailto:Poul.Bak.Thorsen@slb.regionsyddanmark.dk). An internet search for Poul Bak Thorsen found that Thorsen continues his involvement in research, but is now referred to as “Poul Bak Thorsen” or “PB Thorsen.” His research team provided a poster session at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) in early March in San Diego. It is unclear whether Dr. Thorsen came to the United States himself (since the Department of Justice has extradition orders for him with the Danish government to face criminal charges).



## Background Report Regarding Poul Thorsen, MD

Widely announced in early March in Denmark, the Aarhus University will receive a grant for the project to be known as 'The Lundbeck Foundation's Initiative for Integrative Psychiatric Research' (iPSYCH). The grant of DKK 121m (approximately \$21.5 million) from the Lundbeck Foundation is the largest grant ever awarded to Danish psychiatric research. It will look at five mental health conditions including autism's connections between genetics and the environment.(Exhibit 15)

The Lundbeck Foundation is a commercial foundation that holds 70% of the shares in the Lundbeck Group, a global pharmaceutical company working on brain disorders. Lundbeck Group has at least eight mental health drugs in phase II and III development stages with two in registration process.

A Lise Bech Jellesmark - Thorsen is listed as a PhD research student at a Lundbeck Foundation activity at Aarhus. It is unclear if there is a relationship between Lisa and Poul at this time. (Exhibit 16)

The North Atlantic Neuro-Epidemiology Alliances, Department of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark (referred to as NANEA) received \$16 million in grant funds from the CDC. A March 2010 article in a Danish newspaper (Exhibits 17 and 18) details how the project was 'gold plated' because of the American money, and due to its funding it grew larger than the actual Department of Epidemiology at the university and thus moved to its own headquarters. The article states, *"In the first years of the employees live in a world of glitz and pampering. "We run in a huge Mercedes! 'Is the watchword, and it's true. Every time a scientist travels into the country to gather data, it is in business class, says Anja. Lise says that the Danes are visiting in Atlanta, where they are impressed when a limousine rolls up in front of the hotel door to take them to meetings with the CDC. Delicious dinners, expensive brands of alcohol and stay in luxury get-aways as Denmark's castles are on the program when the traffic goes the other way and money the men from the USA visiting Denmark."*

This article implies there may have been other interests involved in NANEA (which may have created a financial conflict of interest on the CDC funded grants) and states that several of the employees were paid sums in addition to their government salary, an action that is considered illegal in Denmark. A timeline of potential interest is also provided in the article:

### ***NANEA Rise and Fall (Exhibit 17)***

2000	NANEA created with CDC grant of \$7.8 million (Poul Thorsen to run)
2007	CDC provides another \$ 8.2 million.
2008	Poul Thorsen moved to Atlanta, but remained as scientific and administrative head of NANEA
Winter 2008-2009	AU discovers there are no funds for research done at NANEA. Poul Thorsen assures them money will come from the U.S. and provides declarations of grants as documentation.
March 2009	Poul Thorsen resigns his position at Aarhus University. NANEA disbanded, but projects

## Background Report Regarding Poul Thorsen, MD

	continue under new management.
Spring 2009	University of Aarhus discovers three letters acknowledging grants from the CDC were apparently falsified, just as the CDC does not acknowledge a letter on an outstanding amount of NANEA first appropriation. In all, falsified signatures appear on documents totaling nearly two million dollars.
May 2009	Science, Technology and Innovation Council submit a police report. The notification is not directed against any named person.
Fall 2009	University of Aarhus discovers that Poul Thorsen has maintained a dual appointment as associate professor in Denmark and a professor at Emory University in Atlanta that the University of Aarhus did not approve.
January 2010	University of Aarhus director Jorgen Jorgensen denounces Poul Thorsen in a message to Nanea-project partners. The message also mentions the fraud case.
February 2010	Savannah Morning News takes up the case and the other media follow.
March 2010	Østjyllands Police investigators continue to raise a charge against the key person.

Other articles from the same news sources indicate that at least one other scientist is under investigation.

### Conclusions and Questions that Remain

**The Danish Vaccine Studies are Tainted:** Years before the criminal activities came to light studies from Thorsen had been called into question based on conflicts of interest, design flaws and quality issues. These same studies were used by the US government as the basis to refute any link between vaccine injury and the onset of the symptoms of autism spectrum disorders. Congressman David Weldon (Exhibit 19) and a Summary Provided by SafeMinds (Exhibit 20) provide background on these issues.

In the dozen years since the House Committee on Oversight and Government Reform first looked into the government's handling of the epidemic rise in rates of autism spectrum disorder and its possible link to vaccine injury, the CDC became party to a \$16 million investment in Denmark to obtain research studies to exonerate the vaccine program. As much as \$2 million of that investment is alleged to have been absconded by Poul Thorsen, the researcher who came to the CDC as an employee, earned enough trust at the CDC to influence grant direction, and in a breach of federal policy, acted as principal investigator of the program where he had directed the funds. Even after being indicted by the US Government for mail fraud and money laundering, Dr. Thorsen continues to collaborate with at least one CDC employee. Thorsen also faced charges of tax evasion in Denmark which were dismissed for technical reasons (which leaves open for refilling). He continues to be employed in Denmark. The US has yet to extradite him, although he may have entered the US to make a poster session presentation in San Diego in early March 2012.

Many questions remain regarding the gross mismanagement of \$16 million and the management of the criminal case. They include:

**Question:** Can it be that Thorsen acted alone? (Many feel it is unlikely.) Are the CDC and/or Aarhus University seeking to make Thorsen a scape goat?

## Background Report Regarding Poul Thorsen, MD

**Question:** Is it possible for the very same Justice Department that used Thorsen's research against families seeking compensation in the Vaccine Injury Compensation Program to present an unbiased and effective prosecution?

**Question:** Who were the career CDC employees who allowed Dr. Thorsen to become principal investigator of the Denmark study? (Ethically he should not have been allowed to since he played a significant role in developing the grant and seeing it awarded to Denmark. He in essence personally benefited from the grant which he helped direct to Denmark (even before the criminal activity).

**Question:** Does the CDC continue to fund research in Denmark?

**Question:** Who at the CDC/HHS was responsible for overseeing the \$16 million dollar grant to Denmark? How did they not see the fraud?

**Question:** Almost 12 months after the indictment, what is the status of the prosecution?

**Question:** Where in the world is Poul Thorsen now and why has he not been extradited to US?

**Question:** Did Thorsen enter the US in March 2012 unnoticed?

**Congressional Oversight Needed:** The Poul Thorsen management in and of itself calls for oversight. Given the importance the research he was pivotal in managing has played in both the Institute of Medicine's review of the matter as well as the emphasis placed on this data by the government in the Autism Omnibus proceedings of the National Vaccine Injury Compensation Program, an inquiry is urgently needed. Autism has gone from a national epidemic to a national emergency with rates 73% higher than the initial inquiry in 2007 of children born in 1995.<sup>3,4</sup>

The Coalition for SafeMinds and the Elizabeth Birt Center for Law & Advocacy on behalf of the community have asked the Congress to take action on this matter. ([www.safeminds.org](http://www.safeminds.org) & [www.ebcala.org](http://www.ebcala.org))

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<sup>3</sup> The CDC released data in March 2012 indicated the prevalence of autism of children born in the United States in 2000 is 1 in 88, with the rate for boys at 1 in 54. This is a 73 percent increase from their first report in 2007.

<sup>4</sup> While there is no reference to the thimerosal debate in the CDC report, the 2000 US birth cohort would have been exposed to thimerosal in their infant vaccines, while Denmark removed all preservatives from their children's vaccines in 1992.

## Background Report Regarding Poul Thorsen, MD

### Exhibits

<b>1</b>	Announcement by the US Attorney Northern District of Georgia, “Autism Researcher Indicted for Stealing Grant Money”
<b>2</b>	<i>Nature News</i> Published online 20 April 2011   <i>Nature</i> 472, 264-265 (2011)
<b>3</b>	US V Poul Thorsen Case 1:11-cr-00194-UNA Document 1 Filed 04/13/11
<b>4</b>	Online Real Estate Offering for 2657 Briarlake Road Northeast, Atlanta GA 30345
<b>5</b>	Report of Indictment by <i>Natural News</i> “CDC vaccine scientist who downplayed links to autism indicted by DOJ in alleged fraud Scheme”
<b>6</b>	<i>Natural News</i> Graphic Regarding Thorsen
<b>7</b>	2001 Article Identification of biological/biochemical marker(s) for preterm delivery in which Thorsen is listed as corresponding author at the CDC.
<b>8</b>	Thorsen-Schendel of CDC History of Co-Authorship (including after indictment)
<b>9</b>	2010 APA DSM5 Work Group Member Disclosure Report
<b>10</b>	APA DSM5 Conference on Autism and PDD Report
<b>11</b>	Aarhus University January 2010 Statement on Thorsen
<b>12</b>	Blog report from journalist Ulla Danielson reporting that Thorsen Tax Evasion case delayed
<b>13</b>	Blog report from journalist Ulla Danielson reporting that Thorsen Tax Evasion Dismissed for Technical Issues
<b>14</b>	PubMed Biblio of Poul Thorsen
<b>15</b>	iPSYCH Announcement of Funds to Aarhus
<b>16</b>	Lundbeck Foundation Staff List (Another Thorsen Listed)
<b>17</b>	As the Agitator Came to the University (Story About Thorsen/NANEA)
<b>18</b>	As the Agitator Came to the University (Story About Thorsen/NANEA) (The original in Danish)
<b>19</b>	“Something is Rotten, Just Not in Denmark” Remarks of Dr. David Weldon (Member of Congress) in 2004.
<b>20</b>	Vaccines and Autism, What Do Epidemiological Studies Really Tell Us? A Coalition of SafeMinds Paper.

EXHIBIT 1



THE UNITED STATES ATTORNEY'S OFFICE  
NORTHERN DISTRICT of GEORGIA

SEARCH THE SITE

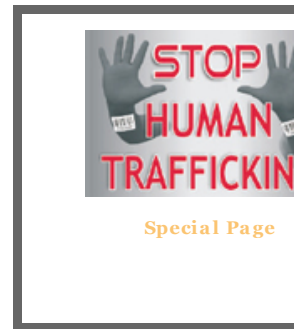
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### AUTISM RESEARCHER INDICTED FOR STEALING GRANT MONEY

FOR IMMEDIATE RELEASE

April 13, 2011

<http://www.justice.gov/usao/gan/>

CONTACT: Patrick Crosby

(404)581-6016

FAX (404)581-6160

#### *Thorsen Allegedly Absconded With Over \$1 Million*

ATLANTA, GA - POUL THORSEN, 49, of Denmark, has been indicted by a federal grand jury on charges of wire fraud and money laundering based on a scheme to steal grant money the CDC had awarded to governmental agencies in Denmark for autism research.

United States Attorney Sally Quillian Yates said of the case, "Grant money for disease research is a precious commodity. When grant funds are stolen, we lose not only the money, but also the opportunity to better understand and cure debilitating diseases. This defendant is alleged to have orchestrated a scheme to steal over \$1 million in CDC grant money earmarked for autism research. We will now seek the defendant's extradition for him to face federal charges in the United States."

"Stealing research grant money to line his pockets, as Poul Thorsen stands accused of here today, cheats U.S. taxpayers and will simply not be tolerated," said Derrick L. Jackson, Special Agent in Charge of the Atlanta Region for the Office of Inspector General of the Department of Health & Human Services. "HHS/OIG will continue to work closely with our law enforcement partners to bring these criminals to justice."

Reginael D. McDaniel, Special Agent in Charge of the Atlanta Region for Internal Revenue Service Criminal Investigation said, "Today's global economy demands a high-level coordinated approach by multiple agencies and authorities in the investigation of financial crimes. While schemes often become more sophisticated over time, fortunately, so do our investigative techniques. IRS Criminal Investigation is proud to have shared its hallmark expertise in following the money trail in the scheme alleged in this indictment."

According to United States Attorney Yates, the charges and other information presented in court: In the 1990s, THORSEN worked as a visiting scientist at the U.S. Centers for Disease Control and Prevention (CDC), Division of Birth Defects and Developmental Disabilities, when the CDC was soliciting grant applications for research related to infant disabilities. THORSEN successfully promoted the idea of awarding the grant to Denmark and provided input and guidance for the research to be conducted. From 2000 to 2009, the CDC awarded over \$11 million to two governmental agencies in Denmark to study the relationship between autism and exposure to vaccines, between cerebral palsy and infection during pregnancy, and between childhood development and fetal alcohol exposure. In 2002, THORSEN moved to Denmark and became the principal investigator for the grant, responsible for administering the research money awarded by the CDC.

Once in Denmark, THORSEN allegedly began stealing the grant money by submitting fraudulent documents to have expenses supposedly related to the Danish studies be paid with the grant money. He provided the documents to the Danish government, and to Aarhus University and Odense University Hospital, where scientists performed research under the grant. From February 2004 through June 2008, THORSEN allegedly submitted over a dozen fraudulent invoices, purportedly signed by a laboratory section chief at the CDC, for reimbursement of expenses that THORSEN claimed were incurred in connection with the CDC grant. The invoices falsely claimed that a CDC laboratory had performed work and was owed grant money. Based on these invoices, Aarhus University, where THORSEN also held a

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federal crimes are treat  
compassion, fairness and

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faculty position, transferred hundreds of thousands of dollars to bank accounts held at the CDC Federal Credit Union in Atlanta, accounts which Aarhus University believed belonged to the CDC. In truth, the CDC Federal Credit Union accounts were personal accounts held by THORSEN. After the money was transferred, THORSEN allegedly withdrew it for his own personal use, buying a home in Atlanta, a Harley Davidson motorcycle, and Audi and Honda vehicles, and obtaining numerous cashier's checks, from the fraud proceeds. THORSEN allegedly absconded with over \$1 million from the scheme.

The indictment charges THORSEN with 13 counts of wire fraud and 9 counts of money laundering. The wire fraud counts each carry a maximum of 20 years in prison, and the money laundering counts each carry a maximum of 10 years in prison, with a fine of up to \$250,000 for each count. The indictment also contains a forfeiture provision seeking forfeiture of all property derived from the offenses, including an Atlanta residence, two cars, and a Harley Davidson motorcycle. In determining the actual sentence, the Court will consider the United States Sentencing Guidelines, which are not binding but provide appropriate sentencing ranges for most offenders.

This case is being investigated by Special Agents of the Office of Inspector General of the Department of Health & Human Services and the Internal Revenue Service Criminal Investigation Division.

Assistant United States Attorneys Stephen H. McClain and Michael J. Brown are prosecuting the case.

Members of the public are reminded that the indictment contains only allegations. A defendant is presumed innocent of the charges and it will be the government's burden to prove a defendant's guilt beyond a reasonable doubt at trial.

For further information please contact Sally Q. Yates, United States Attorney, or Charysse L. Alexander, Executive Assistant United States Attorney, through Patrick Crosby, Public Affairs Officer, U.S. Attorney's Office, at (404) 581-6016. The Internet address for the HomePage for the U.S. Attorney's Office for the Northern District of Georgia is [www.justice.gov/usao/gan](http://www.justice.gov/usao/gan).

[Return to Top](#)



- HOME
- ABOUT
  - Our Office
  - FAQ's
- NEWS
  - Press Releases
- MEET THE US ATTORNEY
- DIVISIONS & BRANCH OFFICES
  - Criminal
  - Civil
  - Administrative
- PROGRAMS
  - LECC
  - PSN
  - Information for Victims & Witnesses
  - Weed & Seed
- CAREERS
- CONTACT
  - Telephone
  - Mail
  - Webmaster

- Site Map
- Accessibility
- FOIA
- Privacy Policy
- Legal Policies & Disclaimers

EXHIBIT 2



Published online 20 April 2011 | *Nature* **472**, 264–265 (2011) | doi:10.1038/472264a

Seven Days

## Seven days: 15–21 April 2011

The week in science.



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### Policy

**Wolf delisted** The grey wolf will be removed from the US government's endangered species list in some northwestern states as a result of a policy initiative tagged on to the US federal budget bill, which was approved last week. Grey wolf populations have recovered significantly in northwestern states, but environmental campaigners such as the Center for Biological Diversity in Tucson, Arizona, bemoaned the fact that politicians had lifted protection rather than waiting for due process under the Endangered Species Act. For details of the budget's settlement for science, see [page 267](#).

**Israel to join CERN** Israel is set to become the first non-European member of CERN, Europe's high-energy physics research centre near Geneva, Switzerland. On 17 April, Israel's cabinet voted to join the lab. Full membership has historically been limited to European nations, but last June, CERN's council opened the door to outsiders. The council is expected to approve Israel's membership in an upcoming meeting. Brazil, Cyprus, Serbia, Slovenia and Turkey are also pursuing full membership.

**Hormones in sport** Female athletes may not be eligible to compete as women if blood tests show they have natural testosterone levels in the male range, according to rules accepted by the

International Association of Athletics Federations on 12 April. The decision on hyperandrogenism — in which the body produces higher than normal levels of androgen hormones, particularly testosterone — has been broadly welcomed by experts. See [go.nature.com/xc5cnm](http://go.nature.com/xc5cnm) for more.

**European networks** The European Institute of Innovation and Technology (EIT) said on 14 April that it is considering eight areas — including biotechnology, smart cities and ageing — in which to fund new collaborative research networks. It already funds three such initiatives, known as Knowledge and Innovation Communities (KICs), focusing on topics including climate change. These are networks of industry and academic partnerships with EIT funding of €308.7 million (US\$439 million) to 2013. Any new plans will feed into the European Commission's own proposals for the EIT's future, which are due in December. On 14 April the commission launched a public consultation on the subject.

**Shuttles at rest** The four remaining vehicles of the US Space Shuttle fleet were assigned their final resting places on 12 April. *Atlantis* will remain at the Kennedy Space Center in Merritt Island, Florida; *Endeavour* will head to the California Science Center in Los Angeles; and *Discovery* will go to the Steven F. Udvar-Hazy Center in Chantilly, Virginia, which is part of the National Air and Space Museum in Washington DC. A flight test vehicle, *Enterprise*, will travel to the Intrepid Sea, Air & Space Museum in New York City. See [go.nature.com/tiilci](http://go.nature.com/tiilci) for more.

**Virus sharing** In the event of a future flu pandemic, member states of the World Health Organization (WHO) will send samples of flu virus to laboratories and drug makers around the world, in return for greater access to any vaccines created. The deal, announced by the WHO on 17 April, heads off the prospect of countries refusing to share samples with WHO laboratories in protest at not benefiting from resulting research patents or vaccines — as Indonesia did in 2007.

## Events

**Clean-up visions for Fukushima** As workers continue to douse stricken reactors at the Fukushima Daiichi nuclear plant with water, the facility's owner has laid out plans for stabilizing and cleaning up the site. On



executives are pictured at a harried press conference six days earlier) put forward a plan to stabilize the plant within six to nine months. According to this, workers will continue to pump in water to cool three damaged reactors, as well as spent fuel pools, while, in parallel, developing techniques to store and decontaminate used water on the site. The company also plans to cover the damaged reactors with temporary structures in order to limit the release of radioactivity.



AP PHOTO/H. KOMAE

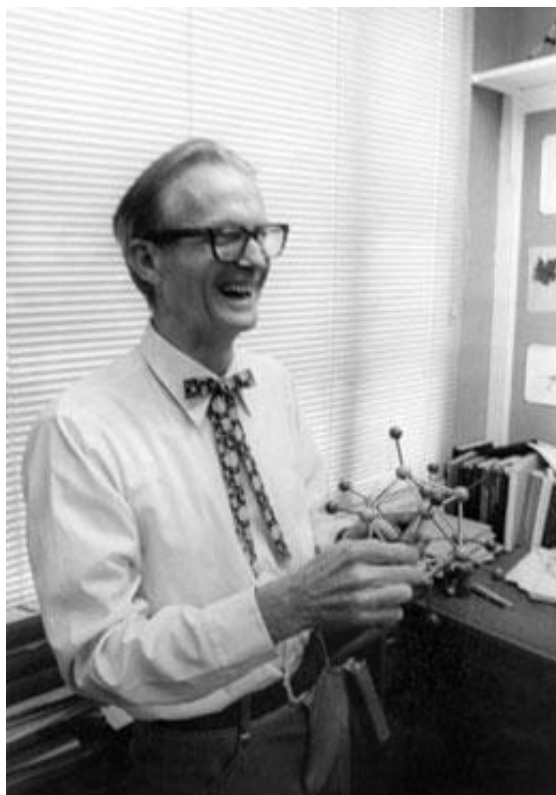
## People

**Research fraud** Prosecutors in the United States are seeking to extradite a Danish scientist researching the relationship between autism and vaccines, who, they allege, stole more than US\$1 million in research funding. Poul Thorsen was a visiting scientist at the Centers for Disease Control and Prevention (CDC) in Atlanta in the 1990s. US prosecutors say that after returning to Denmark in 2002, Thorsen submitted false invoices from the CDC to Aarhus University, which unknowingly transferred funds to his personal account. He was last week charged with 13 counts of wire fraud and 9 of money laundering.

**New chief scientist** Australia's government has appointed Ian Chubb as its chief scientist. Originally a neuroscientist, Chubb has spent the past few decades in senior administration roles at various universities and research councils; most recently, he was vice-chancellor of the Australian National University in Canberra from 2001 to 2010. He replaces Penny Sackett, who in February announced her surprise resignation, halfway through her five-year term. Chubb's three-year term starts on 23 May.

**Lab death** Michele Dufault, a 22-year-old undergraduate student, was found dead after an accident at Yale University's Sterling Chemistry Laboratory on 13 April. See [page 270](#) for more.

**Nobel chemist dies** William Lipscomb, who won the 1976 Nobel Prize in Chemistry for his work on chemical bonding, died on 14 April aged 91. Lipscomb (pictured) helped to elucidate the nature of bonding between molecular clusters of boron and hydrogen atoms — called boranes — which did not obey principles known at the time. After starting out at the University of Minnesota, he moved to Harvard University in Cambridge, Massachusetts, in 1959, where he remained for the rest of his career.



William Lipscomb

*EMILIO SEGRE VISUAL  
ARCHIVES/AM. INST. PHYS./SPL*

## Research

**Brain atlas debuts** A genetic and anatomical map of the human brain, bankrolled by Microsoft co-founder Paul Allen, was officially unveiled on 12 April. The Seattle, Washington-based Allen Brain Science Institute's human brain atlas ([www.brain-map.org](http://www.brain-map.org)) logged gene-expression patterns and biochemical activity at 1,000 locations in brains donated by two people, generating a total of 100 million data points. The US\$55-million project follows a mouse brain atlas, released in 2006, and a map of the mouse spinal cord two years later. See

[go.nature.com/l9923y](http://go.nature.com/l9923y) for more.

## Funding

**Golden rice funds** The Bill and Melinda Gates Foundation is giving US\$18.6 million to research on transgenic, nutritionally fortified rice and cassava. The International Rice Research Institute in Los Baños, the Philippines, won \$10.3 million to develop golden rice, which delivers extra vitamin A; it hopes that the rice will receive regulatory approval in the Philippines in 2013 and in Bangladesh in 2015. The Donald Danforth Plant Science Center in St Louis, Missouri, was given \$8.3 million for work on BioCassava Plus, which contains extra vitamin A, iron and protein. The centre hopes the enhanced cassava will gain approval in Kenya and Nigeria by 2017. See [go.nature.com/uuyc60](http://go.nature.com/uuyc60) for more.

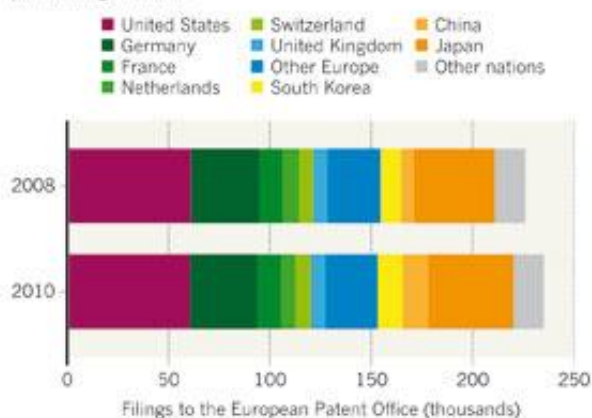
**Chernobyl shelter** An international fund-raising effort to help decommission the Chernobyl nuclear power station in Ukraine seemed on 19 April to have fallen short of its goal. After a meeting in Kiev, Viktor Yanukovich, president of Ukraine, said that world governments and international organizations had pledged an extra €550 million (US\$780 million) to help build a spent-fuel storage facility and an enormous steel arch to cover the shattered reactor — currently surrounded by a crumbling concrete sarcophagus. But the meeting had hoped to raise €740 million to make up the roughly €2-billion cost of this effort. See [go.nature.com/xmmfhk](http://go.nature.com/xmmfhk) for more.

## Trend watch

Patent filings received by the European Patent Office in 2010 topped 235,000, an all-time high. Applications from the European Union and United States slowed in the financial crisis, but have recovered, and filings from China have almost doubled from 6,490 in 2008 to 12,698 in 2010. But China's portfolio is unbalanced: 43% of its applications considered in 2005–10 were in digital and telecommunications, whereas biotechnology — a growing sector for other nations — made up only 3% of claims.

### PATENT FILINGS RESUME GROWTH

A boost from Asia accounted for an upturn in European patent filings in 2010.



[Click for larger version.](#) **SOURCE: EPO**

## Coming up

### 24–29 April

The European Science Foundation is holding a week-long conference devoted to the science and technology of graphene, in Obergurgl, Austria.

[go.nature.com/xnyc4t](http://go.nature.com/xnyc4t)

## 26 April

The 25th anniversary of the nuclear disaster at Chernobyl in what is now Ukraine.

## Comments

---

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*Comments on this thread are vetted after posting.*

---

They don't and this is why i think mccains strategy to win is flawless.He's running so much #31503  
negative stuff on obama until obama has to spend most of his time defending himself thus meaning mccain  
has yet to talk about his plans for the economyhealthcare or any of that stuff.And to think people have the  
nerve to say whats obama's plan.Whats Mccains except talking about war? [rio sfr](#)

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Posted by: [Ashra Rio](#) | 2011-11-30 08:53:15 AM

---

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EXHIBIT 3



**FILED IN CHAMBERS**  
U.S.D.C. Atlanta

**ORIGINAL**

IN THE UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF GEORGIA  
ATLANTA DIVISION

APR 18 2011

JAMES N. HATTEN, Clerk  
By: *James N. Hatten*  
Deputy Clerk

UNITED STATES OF AMERICA :  
 :  
 v. :  
 :  
 POUL THORSEN :

CRIMINAL INDICTMENT

NO. **1:11-CR-194**

THE GRAND JURY CHARGES THAT:

COUNTS ONE THROUGH THIRTEEN  
(Wire Fraud)

1. Beginning on a date unknown, but at least by in or about February 2004, and continuing until in or about February 2010, in the Northern District of Georgia and elsewhere, the defendant, POUL THORSEN, aided and abetted by others known and unknown to the Grand Jury, did knowingly devise and intend to devise a scheme and artifice to defraud, and to obtain money and property by means of materially false and fraudulent pretenses, representations, and promises, and by omission of material facts, well knowing and having reason to know that said pretenses, representations, and promises were and would be false and fraudulent when made and caused to be made and that said omissions were and would be material.

2. Beginning in or about 2000, the U.S. Centers for Disease Control and Prevention (CDC), Division of Birth Defects and Developmental Disabilities, awarded grant money to Denmark for research involving infant disabilities, autism, genetic disorders,



and fetal alcohol syndrome. The CDC awarded the grant to fund studies of the relationship between autism and the exposure to vaccines, the relationship between cerebral palsy and infection during pregnancy, and the relationship between developmental outcomes and fetal alcohol exposure.

3. Defendant THORSEN worked as a visiting scientist at the CDC, Division of Birth Defects and Developmental Disabilities, when the CDC was soliciting the grant applications. Defendant THORSEN promoted the idea of awarding the grant to Denmark for studies related to infant disabilities. Defendant THORSEN scheduled meetings with the Danish Medical Research Council, Aarhus University, and Odense University Hospital about the proposed Danish research. In addition to initiating the meetings, defendant THORSEN provided guidance and ideas for the grant that the CDC ultimately awarded to Denmark.

4. The CDC initially awarded the grant to the Danish Medical Research Council and then, beginning in or about 2007, to the Danish Agency for Science, Technology and Innovation (DASTI), both of which were governmental agencies in Denmark. From 2000 through 2009, the CDC awarded over \$7 million to the Danish Medical Research Council and over \$4 million to DASTI, totaling over \$11 million, for the Danish research studies.

5. Aarhus University and Odense University Hospital administered the CDC grant under the direction of a principal

investigator, who was assigned scientific and administrative oversight.

6. In 2002, after CDC awarded the grant, defendant THORSEN went to Denmark and became the principal investigator, responsible for administering the research money awarded by the CDC to Denmark. Defendant THORSEN also held a faculty position at Aarhus University, where scientists performed research under the grant. In those positions, he submitted invoices for payment to Aarhus University and Odense University Hospital for work and expenses related to the CDC grant.

7. In or about May 2007 and March 2008, defendant THORSEN submitted fraudulent letters to DASTI, purportedly signed by grant management officers at the CDC, that falsely stated that the CDC had awarded grant money, and that certain funds were available, to DASTI under the grant. Defendant THORSEN forged the CDC employees' signatures on the letters. Based on the misrepresentations in these letters, DASTI released funds for work and expenses that defendant THORSEN claimed were associated with the CDC grant.

8. From in or about February 2004 through in or about June 2008, defendant THORSEN submitted over a dozen fraudulent invoices, purportedly signed by a laboratory section chief at the CDC's National Center on Birth Defects and Developmental Disabilities, for reimbursement of expenses that defendant THORSEN claimed were incurred in connection with the CDC grant. The invoices falsely

claimed that a CDC laboratory had performed work under the grant for which Aarhus University owed money. Based on the misrepresentations in these invoices, Aarhus University wire transferred hundreds of thousands of dollars to accounts held at the CDC Federal Credit Union in Atlanta, Georgia. Aarhus University believed that the accounts, which were identified in the fraudulent invoices, belonged to the CDC.

9. In truth, the CDC Federal Credit Union accounts were personal accounts held by defendant THORSEN. He used the accounts to steal money under the CDC grant.

10. After the money was transferred to defendant THORSEN's accounts, he moved the money among multiple CDC Federal Credit Union accounts and eventually withdrew it for his own personal use. Defendant THORSEN purchased a home in Atlanta, a Harley Davidson motorcycle, and Audi and Honda vehicles with the proceeds of his fraud. He also obtained numerous cashier's checks made out to himself from the fraudulent proceeds deposited at the CDC Federal Credit Union.

11. Defendant THORSEN obtained over \$1 million from his scheme to defraud.

12. On or about the dates set forth below, in the Northern District of Georgia and elsewhere, the defendant, POUL THORSEN, aided and abetted by others known and unknown to the Grand Jury, and for the purpose of executing the aforementioned scheme and

artifice to defraud, transmitted and caused to be transmitted by means of wire communication in interstate and foreign commerce, writings, signs, signals, and sounds, that is, wire transfers in the following amounts from accounts held by Aarhus University in Denmark to accounts held by defendant THORSEN at the CDC Federal Credit Union in Atlanta, Georgia:

COUNT	DATE	AMOUNT
1	12/4/2006	\$24,708.00
2	1/16/2007	\$43,406.00
3	2/22/2007	\$30,409.00
4	3/15/2007	\$56,506.00
5	3/22/2007	\$17,520.00
6	6/18/2007	\$121,961.00
7	1/16/2008	\$47,171.76
8	4/1/2008	\$47,219.00
9	5/2/2008	\$65,928.00
10	6/26/2008	\$23,602.00
11	6/26/2008	\$23,602.00
12	10/29/2008	\$23,602.00
13	10/29/2008	\$23,602.00

All in violation of Title 18, United States Code, Sections 1343 and 2.

**COUNTS FOURTEEN THROUGH TWENTY-TWO**  
**(Money Laundering)**

13. The Grand Jury re-alleges and incorporates by reference paragraphs 1 through 11 of this Indictment as if fully set forth

herein.

14. On or about the dates set forth below, in the Northern District of Georgia and elsewhere, the defendant, POUL THORSEN, aided and abetted by others known and unknown to the Grand Jury, knowingly engaged in and attempted to engage in the monetary transactions described below in criminally derived property of a value greater than \$10,000, consisting of the deposit, withdrawal, transfer, and exchange, in and affecting interstate and foreign commerce, of funds and monetary instruments by, through, and to a financial institution, such property having been derived from specified unlawful activity, that is, a scheme to defraud in violation of Title 18, United States Code, Sections 1343 and 2:

COUNT	DATE	TRANSACTION	AMOUNT	PAYEE
14	5/30/2006	Withdrawal by personal check from CDC Federal Credit Union (FCU) account no. ending 3353	\$33,994.57	Stone Mountain Harley Davidson
15	7/27/2006	Withdrawal by cashier's check from CDC FCU account no. ending 0698	\$52,892.25	THORSEN
16	12/5/2006	Transfer from CDC FCU account no. ending 1335	\$19,071.00	J.H. (CDC FCU account no. ending 0698)
17	1/17/2007	Transfer from CDC FCU account no. ending 1335	\$19,271.00	J.H. (CDC FCU account no. ending 0698)

18	3/16/2007	Transfer from CDC FCU account no. ending 8562	\$56,400.00	THORSEN (CDC FCU account no. ending 1335)
19	6/26/2007	Withdrawal by cashier's check from CDC FCU account no. ending 0698	\$17,338.00	THORSEN
20	5/5/2008	Transfer from CDC FCU account no. ending 1335	\$21,746.56	THORSEN (CDC FCU account no. ending 2920)
21	6/30/2008	Withdrawal by cashier's check from CDC FCU account no. ending 0698	\$11,041.00	THORSEN
22	10/29/2008	Transfer from CDC FCU account no. ending 8562	\$47,200.00	THORSEN (CDC FCU account no. ending 1335)

All in violation of Title 18, United States Code, Sections 1957 and 2.

FORFEITURE PROVISION

15. Upon conviction of one or more of the wire fraud offenses alleged in Counts 1 through 13 of this Indictment, in violation of Title 18, United States Code, Section 1343, the defendant, POUL THORSEN, shall forfeit to the United States, pursuant to Title 18, United States Code, Sections 981(a)(1)(C), 1956(c)(7), and 1961(1), and Title 28, United States Code, Section 2461(c), any property, real or personal, which constitutes or is derived from proceeds traceable to such offenses, including but not limited to the following:

(A) MONEY JUDGMENT

A sum of money equal to the amount of proceeds the defendant obtained as a result of the offenses.

(B) REAL PROPERTY

- (1) 2657 Briarlake Road, Atlanta, DeKalb County, Georgia 30345, and all buildings and appurtenances thereon, more particularly described as follows:

All that tract or parcel of land lying and being in Land Lot 206 of the 18th District, DeKalb County, Georgia, and being Lot 31, The Woods of Briarlake as per plat recorded in Plat Book 90, Page 72, DeKalb County, Georgia records, which plat is incorporated herein and made a part hereof by reference.

(C) CONVEYANCES

- (1) 2008 Honda CR-V EX-L, VIN 5J6RE48728L040280.
- (2) 2004 Audi S4 Avant Quattro, VIN WAUXL68E84A145888.
- (3) 2006 FLSTFSE2 Harley Davidson motorcycle, VIN 1HD1PNF146Y955597.

16. Upon conviction of one or more of the money laundering offenses alleged in Counts 14 through 22 of this Indictment, in violation of Title 18, United States Code, Section 1957, defendant THORSEN shall forfeit to the United States, pursuant to Title 18, United States Code, Section 982(a)(1), any and all property, real or personal, involved in such offenses and all property traceable to such offenses, including but not limited to the following:

(A) MONEY JUDGMENT

A sum of money equal to the total value of property involved in each offense for which defendant THORSEN is liable.

(B) REAL PROPERTY

- (1) 2657 Briarlake Road, Atlanta, DeKalb County, Georgia 30345, and all buildings and appurtenances thereon, more particularly described as follows:

All that tract or parcel of land lying and being in Land Lot 206 of the 18th District, DeKalb County, Georgia, and being Lot 31, The Woods of Briarlake as per plat recorded in Plat Book 90, Page 72, DeKalb County, Georgia records, which plat is incorporated herein and made a part hereof by reference.

(C) CONVEYANCES

- (1) 2008 Honda CR-V EX-L, VIN 5J6RE48728L040280.
- (2) 2004 Audi S4 Avant Quattro, VIN WAUXL68E84A145888.
- (3) 2006 FLSTFSE2 Harley Davidson motorcycle, VIN 1HD1PNF146Y955597.

17. If, as a result of any act or omission of defendant THORSEN, any property subject to forfeiture:

- (a) cannot be located upon the exercise of due diligence;
- (b) has been transferred or sold to, or deposited with, a third person;
- (c) has been placed beyond the jurisdiction of the Court;
- (d) has been substantially diminished in value; or
- (e) has been commingled with other property which cannot be subdivided without difficulty;

the United States intends, pursuant to Title 21, United States Code, Section 853(p), as incorporated by Title 18, United States Code, Section 982(b) and/or Title 28, United States Code, Section



2461(c), to seek forfeiture of any other property of defendant THORSEN, up to the value of the above forfeitable property.

A True BILL

Ann C Austin  
FOREPERSON

SALLY QUILLIAN YATES  
UNITED STATES ATTORNEY

*Stephen H. McClain*

STEPHEN H. McCLAIN  
ASSISTANT UNITED STATES ATTORNEY  
600 U.S. Courthouse  
75 Spring Street, S.W.  
Atlanta, GA 30303  
404/581-6288  
Georgia Bar No. 143186

EXHIBIT 4



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Status: **Off Market**  
 Bedrooms: **4**  
 Bathrooms: **5**  
 Property type: **Single-Family Home**  
 Size: **2,688 sqft**  
 Lot: —  
 Year built: **1990**  
 Zip: **30345**

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Description provided by Trulia

This is a Single-Family Home located at 2657 Briarlake Road Northeast, Atlanta GA. 2657 Briarlake Rd NE has 4 beds, 5 baths, and approximately 2,688 square feet. The property was built in 1990. The average list price for similar homes for sale is \$326,553 and the average sales price for similar recently sold homes is \$383,200. 2657 Briarlake Rd NE is in the 30345 ZIP code in Atlanta, GA. The average list price for ZIP code 30345 is \$360,790.

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### Public Records for 2657 Briarlake Rd NE

Official property, sales, and tax information from county (public) records as of 11/2011:

- Single Family Residential
- 2,688 sqft
- Stories: 2 story
- Parking Spaces: 2
- Construction: Masonry
- County: DeKalb
- 4 Bedrooms
- Lot Size: 0.16 acres
- A/C
- Exterior Walls: Stucco
- Foundation: Concrete
- Tax Rate Code Area: 4
- 5 Bathrooms
- Built In 1990
- Parking: Garage
- 1 Unit
- Fireplace

### Property Taxes for 2657 Briarlake Rd NE

Year	Value	Land		Improvements	Total	Tax
2011	Market	\$160,200	+	\$386,500	= \$546,700	
2011	Assessed				\$218,680	\$7,608

Source: Public Records

### Request an estimate



Name:

Email:

Phone: (optional)

**Message:** I would like to request a professional estimate for this home 2657 Briarlake Road Northeast, Atlanta GA with 4 bedrooms and 5 bathrooms. Please see more information about home prices at [this link](#).

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---	---

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Price History for 2657 Briarlake Rd NE

Alert

Date	Event	Price	Source
08/11/2006	Sold <a href="#">view details</a>	\$455,000	Public records
03/02/1998	Sold <a href="#">view details</a>	\$290,000	Public records

Location Information near 2657 Briarlake Rd NE

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5 for sale properties, \$329,700 average price  
5 sold properties, \$383,200 average price

Atlanta local info

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  Transit

Sold Homes near 2657 Briarlake Rd NE

Address	Distance	Property Type	Sold price	Sold date	Bed	Bath	Sqft
<a href="#">2153 Starfire Dr NE, Atlanta GA</a>	0.08 mi	Single-Family Home	\$438,000	9/16/11	5	4	3,464
<a href="#">2096 Castleway Dr NE, Atlanta GA</a>	0.18 mi	Single-Family Home	\$290,000	9/09/11	4	3	2,228
<a href="#">2101 Castleway Dr NE, Atlanta GA</a>	0.19 mi	Single-Family Home	\$358,000	6/28/11	4	3	2,448
<a href="#">2686 Parkview Dr NE, Atlanta GA</a>	0.23 mi	Single-Family Home	\$450,000	9/09/11	4	4	4,152

2638 Woodwardia Rd NE, Atlanta GA



\$250,000  
4 br / 2 1/2 ba  
2,634 sqft  
Single-Fa

3772 Briarcliff Rd NE, Atlanta GA



\$325,000  
3 br / 2 1/2 ba  
2,016 sqft  
Single-Fa

25 photos

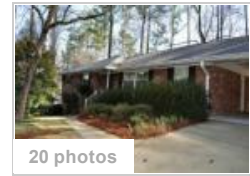
2380 Bradcliff Ct NE, Atlanta GA



\$409,000  
4 br / 3 1/2 ba  
2,089 sqft  
Single-Fa

25 photos

2003 Silvastone Dr NE, Atlanta GA



\$264,500  
3 br / 2 1/2 ba  
1,563 sqft  
Single-Fa

20 photos

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- [2639 Briarlake Rd NE Atlanta, GA](#)
- [2625 Briarlake Rd NE Atlanta, GA](#)
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- [2646 Briarlake Rd NE Atlanta, GA](#)

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EXHIBIT 5

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## CDC vaccine scientist who downplayed links to autism indicted by DOJ in alleged fraud scheme

by Mike Adams, the Health Ranger, NaturalNews Editor

(NaturalNews) CDC researcher Poul Thorsen, who famously headed up the "Denmark Study" that many claim disproved any link between autism and vaccines, has been indicted in Atlanta by a federal grand jury on charges of wire fraud, money laundering and defrauding research institutions of grant money.

Poul Thorson is a scientist who formerly worked for the CDC, and over the last several years, he oversaw millions of dollars in grant money that was used to conduct research to "prove" that vaccines have no link to autism. Dr. Thorson's research papers include the famous "Danish Study" entitled *Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data*. (<http://www.ncbi.nlm.nih.gov/pubmed/12949291>)

This paper concludes that thimerosal, the mercury-based preservative used in vaccines around the world, has no statistically significant link to autism. It is one of the key papers used by vaccination proponents who argue that thimerosal is safe to inject into young children. That Poul Thorson's credibility is now being called into question by a federal indictment of fraud and money laundering will, of course, have ripple effects throughout both the vaccine industries and autism support groups (more about that below).

Be sure to see our "Web of Alleged Fraud" chart which accompanies this article:  
<http://www.naturalnews.com/files/Web-of-Alleged-Fraud.pdf>

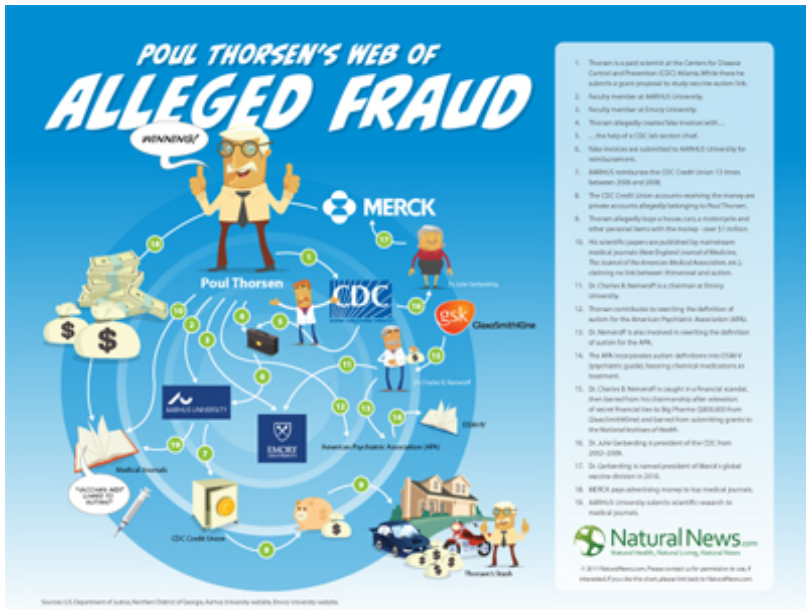
## Follow the money

According to the official announcement of the indictment, Thorsen was awarded grant money by the CDC as far back as the 1990s. He arranged for the grant money to be awarded to an entity in Denmark, where he provided "input and guidance" for the research projects.

From 2000 to 2009, the CDC awarded \$11 million in grant money to two Denmark government agencies to study, among other things, the possible link between vaccines and autism. In 2002, Thorsen moved to Denmark and became the "principal investigator" for the grant money, responsible for administering the research money that the CDC awarded.

But here's where things get interesting: According to the Dept. of Justice, Thorsen began allegedly stealing grant money by **submitting fraudulent expense documents** that were supposedly related to the Danish study. These fraudulent expense documents were given to the Danish government, Aarhus University and Odense University Hospital, the institutions involved in the research.





From February 2004 through June 2008, says the DOJ indictment, Thorsen allegedly submitted over **a dozen fraudulent invoices** requesting reimbursement for expenses that were fabricated. Interestingly, these allegedly fraudulent invoices were **signed by a laboratory section chief at the CDC**, indicating that someone inside the CDC was either duped by Thorsen or potentially involved in the alleged fraud.

What was Thorsen claiming in these allegedly fraudulent invoices requesting reimbursement? He claimed that a **CDC laboratory** had conducted work in conjunction with the research and was owed funds out of the grant money. These invoices were then handed over to Aarhus University, where Thorsen held a faculty

position. Aarhus then transferred "hundreds of thousands of dollars to bank accounts held at the CDC Federal Credit Union in Atlanta," says the DOJ.

But here's the clever part: Those bank accounts were not official CDC accounts at all. They were allegedly **private bank accounts** belonging to none other than Dr. Poul Thorsen.

Once the money was transferred into Thorsen's private accounts, Thorsen "allegedly withdrew it for his own personal use, buying a home in Atlanta, a Harley Davidson motorcycle, and Audi and Honda vehicles, and obtaining numerous cashier's checks, from the fraud proceeds," says the DOJ.

According to government documents, Dr. Poul Thorsen, one of the key researchers in "disproving" any link between vaccines and autism, allegedly defrauded the scientific research community of **over one million dollars**.

See the chart we've assembled for this to help show you the web of money and influence at work here: <http://www.naturalnews.com/files/Web-of-Alleged-Fraud.pdf>

### Aarhus distances itself from Thorsen

More details are revealed through a statement issued in January by Aarhus University, which sought to sever its ties with Thorsen. It says, "Unfortunately, a considerable shortfall in funding at Aarhus University associated with the CDC grant was discovered. In investigating the shortfalls associated with the grant, DASTI and Aarhus University became aware of two alleged CDC funding documents as well as a letter regarding funding commitments allegedly written by Randolph B. Williams of CDC's Procurement Grants Office which was used to secure advances from Aarhus University. Upon investigation by CDC, a suspicion arose that the documents are forgeries." (<http://www.rescuepost.com/files/thorsen-aarhus-1.pdf>)

This letter goes on to state that Dr Thorsen was essentially hoodwinking others into thinking he was still a faculty member at Aarhus University:

*In March 2009, Dr. Thorsen resigned his faculty position at Aarhus University. In the meantime, it has come to the attention of Aarhus University that Dr Thomsen has continued to act in such a manner as to create the impression that he still retains a connection to Aarhus University after the termination of his employment by the university. Furthermore, it has come to the attention of Aarhus University that Dr Poul Thorsen has held full-time positions at both Emory University and Aarhus University simultaneously. Dr Thorsen's double Full-time employment was unauthorised by Aarhus University, and he engaged in this employment situation despite the express prohibition of Aarhus University.*



## The federal indictment against Thorsen

Today, Thorsen is facing **13 counts of wire fraud and 9 counts of money laundering**. NaturalNews spoke with the Department of Justice and confirmed that **extradition proceedings are under way** to bring Thorsen to the United States from Denmark, although no particular timetable for that extradition has been announced.

Thorsen now faces up to **260 years in prison** from the wire fraud charges, and up to an additional 90 years in prison for the money laundering charges, plus a total of \$22.5 million in possible fines. In addition, the federal indictment also contains a so-called "forfeiture provision" which seeks the forfeiture of the personal property Dr. Thorsen allegedly purchased with money he stole from the CDC's grant activities: A house in Atlanta, two cars and a Harley Davidson motorcycle.

The case is being prosecuted by Assistant United States Attorneys Stephen H. McClain and Michael J. Brown, both out of the Northern District of Georgia (Atlanta). This Atlanta office has a well-known reputation for going after crooks, regardless of the political implications. This is the same office, for example, that indicted Atlanta's own mayor for corruption and tax charges in 2004 (<http://www.justice.gov/tax/usaopress/2004/txdv0408-30-04.html>).

The prosecuting attorney for that case, Sally Quillian Yates, is the same attorney contributing to this case. She said of Thorsen: "Grant money for disease research is a precious commodity. When grant funds are stolen, we lose not only the money, but also the opportunity to better understand and cure debilitating diseases. This defendant is alleged to have orchestrated a scheme to steal over \$1 million in CDC grant money earmarked for autism research. We will now seek the defendant's extradition for him to face federal charges in the United States."

Understand what is being alleged here: That Thorsen stole **taxpayer dollars** intended for medical research, then pocketed them in his own private bank accounts and used the money to buy luxury items for his personal use. This is a man with a history of **strong ties to the CDC**, research universities and medical journals. This is a person whose research has been widely quoted by the vaccine apologists who say vaccines are safe. And now, in the midst of all this, how many mainstream newspapers do you see covering Thorsen's indictment and his ties to the CDC? **Virtually none.**

This is the great untold story of **an alleged criminal ring operating inside the CDC**, with the purpose of falsifying research that would "disprove" any links between vaccines and toxic side effects.

## The upshot of all this

What you read above are the facts of the case. What you're about to read is my own opinion analysis as the editor of NaturalNews. While I spoke with the U.S. Attorney's Office on these matters, what you're about to read are my own opinions, not theirs.

For starters, given that the Journal of the American Medical Association (JAMA), the New England Journal of Medicine (NEJM), the American Journal of Epidemiology and many other medical journals have published Dr. Thorsen's work, will they *retract* his scientific papers now that he has been indicted for fraud and money laundering?

Or do the medical journals only retract papers only from those whose research suggests that vaccines do, in fact, have a link to intestinal disorders and neurological problems in children? Remember, of course, that the conventional medical industry almost couldn't wait to denounce Dr. Andrew Wakefield's research, based on only the flimsiest of allegations which don't even stand up to basic scrutiny. And yet when one of their own "insider" scientists like Dr. Poul Thorsen is indicted for fraud and money laundering, they don't question the integrity of his scientific research in the least. In fact, the CDC is now publicly defending his research! His research is still openly cited on the CDC's own website! (<http://www.cdc.gov/ncbddd/autism/articles.html>)

So don't hold your breath waiting for the medical journals to denounce Dr. Thorsen's research. His so-called "scientific findings" are such an important cornerstone in the false "scientific" evidence dispelling any link between vaccines and autism that they would probably let his research stand even if he was convicted of rape, murder and incest. No criminal is too criminal for the medical journals, it seems -- especially if his

conclusions support the vaccine industry.

Secondly, did you notice that the allegedly falsified invoices submitted by Dr. Thorsen to Aarhus University were signed off by **a CDC lab section chief?** Someone inside the CDC, in other words, was enabling Dr. Thorsen to allegedly engage in this fraud. The question is: Was this person a co-conspirator?

To answer all this, you have to keep one thing in perspective: During the years of 2006 - 2008 when all this alleged fraud was taking place, the vaccine industry was under increasing attack by scientists who questioned their safety. The evidence linking vaccines with autism and gastrointestinal disorders was becoming increasingly evident and increasingly difficult to cover up. Dr. Julie Gerberding was at the help of the CDC, and she was no doubt trying to impress her future employers at Merck, where she is now the president of Merck's global vaccine division, having left the CDC the very next year following Dr. Thorsen's alleged money laundering scheme.

Question: Did the CDC actively enable and support Dr. Thorsen's alleged fraud in order to "pay him off" for falsifying the research that would supposedly disprove any link between vaccines and autism? And was this being masterminded by Dr. Julie Gerberding as part of her effort to prove her loyalty to Merck, where she now runs the global vaccine division?

Consider the ties here: Dr. Poul Thorsen used to have a CDC email address (pct9@cdc.gov). He was on the CDC payroll and spoke at CDC events. He had a private bank account at the CDC Credit Union!

Dr. Thorsen had enough pull with the CDC to get his pet grant project approved, even to the point of having the money wired overseas to a university in Denmark where -- guess what? -- he just happened to be a faculty member with "oversight" of where the money went. For Dr. Thorsen to have pulled off his alleged fraud, he would have needed help **from inside the CDC** -- from the "lab section chief" who signed his invoices that were submitted to Aarhus University for "reimbursement." Those funds, of course, were then allegedly used by Dr. Thorsen to purchase a home, cars and a motorcycle, among other things.

## Was Thorsen a patsy for a larger scheme?

I see two possibilities here: Either the CDC **conspired with Dr. Thorsen**, or they set him up to take the fall. Every great scam needs a fall guy, you see, and the vaccine industry's fraudulent scientific cover-up of the truth about vaccine dangers is one of the greatest scams ever pulled off in the history of human civilization. The CDC has its fingerprints all over this case, as a former employer of Thorsen, the source of the money (which is really taxpayer money, of course), and even the source of the "lab section chief" employee who allegedly helped make all this happen.

To believe that the CDC may have conspired with Dr. Thorsen is not even a stretch. The CDC, as we've already shown, is deeply in bed with the vaccine industry and the drug companies. That's why the former head of the CDC is now the president of Merck's vaccine division ([http://www.naturalnews.com/027789\\_Dr\\_Julie\\_Gerberding\\_Merck.html](http://www.naturalnews.com/027789_Dr_Julie_Gerberding_Merck.html)). It's also why the CDC urges everyone to "get vaccinated" at the first sign of a seasonal flu or an emerging epidemic. The pro-vaccine bias of the CDC has been blatant for years.

## Other CDC scientists also involved in the fraud?

Writers Dan Olmsted and Mark Blaxill from the AgeOfAutism.com website have done additional research on this point, and they've found some solid evidence that should raise questions about the CDC's involvement in Thorsen's alleged fraud. As they published recently in an article entitled *Poul Thorsen's Mutating Resume*: (<http://www.ageofautism.com/2010/03/poul-thorsens-mutating-resume.html>)

*In addition, several current CDC employees including Drs. Diana Schendel, Marshalyn Yeargin-Allsopp and Catherine Rice were affiliated with Thorsen's now-defunct research group. Age of Autism has obtained Internet-archived pages from the Web site of the North Atlantic Neuro-Epidemiology Alliances (NANEA) that list the members of the "Atlanta autism team" including Schendel, Yeargin-Allsopp and Rice, all of whom have been in leadership positions in the CDC's autism epidemiology projects. Schendel is described as NANEA's "coordinator at Centers for Disease Control and Prevention, Atlanta, USA."*

This article goes on to say, by the way, that Thorsen was also working with the American Psychiatric Association (APA) to alter the definition of "autism" in the DSM-V (the psychiatric industry's bible of diagnosis and treatment).

The CDC, of course, has downplayed the whole thing. It released a statement that attempted to characterize Poul Thorsen's alleged fraud as a "fiscal" matter, not something involving his science, as if to imply that a man can be a crook when it comes to his money, but an angel when it comes to his science.

They said:

*"CDC is aware of the allegations by Aarhus University against Poul Thorsen, a Danish doctor who participated in CDC funded research. For the past 10 years, CDC has had a cooperative agreement with the Danish Agency for Science, Technology and Innovation (DASTI) and Aarhus University in Denmark to conduct research studies on issues such as cerebral palsy, autism, alcohol use in pregnancy and Down syndrome. Dr. Thorsen was one of many co-authors on these research projects. All of these were subject to extensive peer review and we have no reason to suspect that there are any issues related to the integrity of the science. The allegations that are fiscal in nature against Dr. Thorsen are being looked into by appropriate authorities."*

(<http://www.ageofautism.com/2010/03/copenhagen-police-investigating-autism-vaccine-researcher-dr-poul-thorsen-for-fraud.html>)

But the other possibility in all this is that someone inside the CDC wanted to protect the CDC's reputation from all the quackery and fraud they saw happening there. Perhaps they were clued in to Dr. Thorsen's alleged money laundering, and they were sick of it. Maybe they saw Dr. Gerberding collect a multi-million-dollar salary from Merck while the rest of the people were left behind at the CDC collecting government wages. This is conjecture, of course, but it seems reasonable to suppose that someone from within the CDC could be the whistleblower on all this.

And if that someone reads this, we want to hear from you. Feel free to leak internal documents to NaturalNews any time you want, through our public feedback form. We protect the identities of all our sources and we are interested in **seeing justice served**. If there is an element in the CDC that is knowingly engaged in criminal fraud and conspiracy, that element needs to be exposed and removed from the CDC for the good of the entire institution. Otherwise, more of this kind of news will only come out in the years ahead, and the reputation of the CDC will only continue to plummet.

Don't think the world isn't noticing already: Just two years ago, the CDC's reputation was relatively high even among natural health practitioners. But after watching the CDC's behavior through these last couple of flu scares, more intelligent people now fully realize the CDC has become little more than **a mouthpiece for the pharmaceutical industry**. It was the CDC, after all, that helped hype up the Swine Flu scare that resulted in billions of taxpayer dollars being needlessly spent on vaccines which were mostly thrown away unused after the scare passed.

## The DOJ earns street cred

The real hero in all this, it turns out, is the **Department of Justice** (DOJ). Rather than bowing to the profit interests of the vaccine industry, the DOJ is going after Dr. Poul Thorsen based solely on his alleged criminal behavior, not based on politics or science. It's refreshing to know that some elements of the federal government are actually doing good work. I've seen this before from the DOJ in its indictments of various pharmaceutical companies, and I continue to believe that the DOJ may be the last remaining hope for justice at the federal level.

I did tell my contact at the DOJ, however, that they should watch out for pressure from the vaccine industry. There will be efforts made, no doubt, to limit the exposure of this case to only Dr. Poul Thorsen and *not involve any other CDC employees* or officials. Honestly, in talking to the DOJ about this case, I think they vastly underestimate the level of commitment the drug companies have to their vaccine profit machine; meaning they also vastly underestimate the tactics that are traditionally used by these companies to limit their damage.

For example, most NaturalNews readers know full well that I've had multiple threats placed on my life, I've

been stalked, I've been impersonated, and there have been assassination attempts made on other leaders in the natural health movement who have dared to question vaccines. What the DOJ doesn't know (but I hope they will soon realize) is that the drug companies will stop at nothing to get their way: They will poison your dog, hack your website, threaten your family, leave nasty notes in your mailbox, plant fake bombs under your car and do whatever else it takes to get you to back off.

I know that DOJ prosecutors and attorneys will be reading this, so let me share something with you that you need to know: When you go up against the pharmaceutical industry, you are doing battle with what is essentially **organized crime**. We're talking a modern-day mob here, and they will not hesitate to engage in attempted bribery, corruption or threats of violence to get their way. If the DOJ begins to uncover a deeper connection between Thorsen, the CDC and the drug companies, beware of the backlash headed your way from both the industry and even the top folks in D.C. The depth of the fraud and crimes being committed right now in the pursuit of vaccine profits is nothing short of astonishing. We've reported on many here at NaturalNews, and yet we've just barely scratched the surface of the real story.

Even the vaccine pushers in the online world engage in precisely the same kind of criminal behavior; fixing online polls, creating robots to maliciously attack anti-vax websites, engaging in the widespread posting of false information, and so on. This is, of course, a reflection of the exact same psychopathic criminal-minded behavior found inside the vaccine industry itself -- an industry staffed by sick-minded human beings who belong in federal prison, not running research for the CDC.

As the editor of NaturalNews, I have publicly, on numerous occasions, called for the Department of Justice to investigate the CEOs of drug companies for fraud, racketeering and conspiracy. While this indictment of Dr. Poul Thorsen isn't all that, it's at least a step in the right direction that may help uncover the truth about what really goes on behind the scenes with taxpayer "research money."

## How much vaccine research is based on outright fraud?

It also raises the question: How many other scientific researchers and grant money administrators are on the take, pocketing taxpayer dollars that were intended for research purposes? How many of these people falsify their research data in order to keep getting grant money injections into their private bank accounts? Just how deep does the collusion between the corrupt scientific community and the fraudulent vaccine industry really go?

And, of course, what is the CDC's role in all this? It has been one of the top cheerleaders for the vaccine industry for at least the past decade. Now, we are learning that a CDC section chief knowingly or unknowingly colluded with a physician and researcher who has now been indicted for fraud and money laundering. How high up the CDC does this alleged fraud really go?

I don't know the answer to that. But it's not that complicated to figure out, especially when CDC employees become Big Pharma vaccine employees, and vice-versa. It's all a giant government-corporate-medicine orgy where the scientific trust was abandoned long ago in favor of Big Pharma profits.

We'll do our best here at NaturalNews to find out the rest of this story and bring it to you. That's what we do. That's why we're the 4th largest alternative news website in the world (and growing every day). We bring you the news about the fraud and corruption in the pharmaceutical industry that most mainstream media sources won't dare touch. Subscribe to my free daily email newsletter to receive a daily email that I send out, containing links to the top stories you need to know about. It's free, so sign up now at: <http://www.naturalnews.com/readerregistration.html>

By the way, I strongly recommend that you become a regular readers of [www.AgeOfAutism.com](http://www.AgeOfAutism.com) which provides outstanding reporting on these issues. Make that site one of your regular sources of information. You'll be amazed by what they are able to report.

### Additional sources for this story include:

<http://kerboblog.blogspot.com/2010/03/news-flash-cdc.html>

<http://www.bizjournals.com/atlanta/news/2011/04/13/dane-indicted-for-defrauding-cdc.html>

<http://www.ageofautism.com/2011/04/danish-study-cdc-doctor-who-debunked-autism-vaccines-link->

indicted-on-fraud.html

<http://www.reuters.com/article/2011/04/13/us-crime-research-funds-idUSTRE73C8JJ20110413>

[Teach Autistic Children](#) Online NCATE Accredited B.A. & M.S. Degrees in Special Ed. Enroll Now! [www.WGU.edu](http://www.WGU.edu)

[Securitization & Forensic](#) Audits all pool data available 5-7 day turnaround industry's best TPQ [www.MortgageAuditSonline.com](http://www.MortgageAuditSonline.com)

[Immunization Records](#) Access Your Child's Medical Record. Free 1 Month Trial. Signup Now! [www.motherknows.com](http://www.motherknows.com)

[Managing Pork Quality](#) Immunological pig castration. Safe option now approved in U.S. [AnimalHealth.Pfizer.com/Consumers](http://AnimalHealth.Pfizer.com/Consumers)

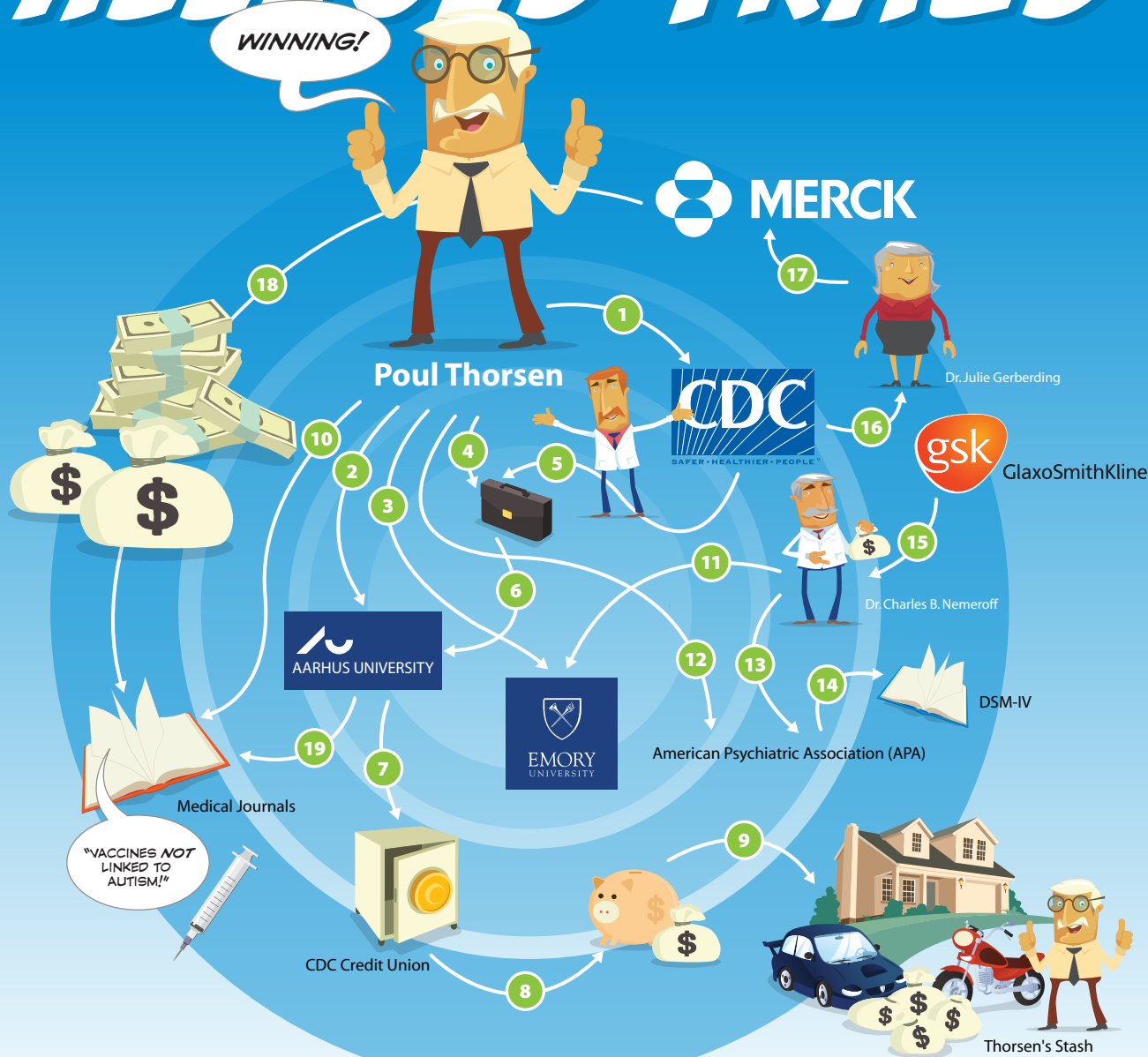
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EXHIBIT 6

# POUL THORSEN'S WEB OF ALLEGED FRAUD



1. Thorsen is a paid scientist at the Centers for Disease Control and Prevention (CDC) Atlanta. While there he submits a grant proposal to study vaccine-autism link.
2. Faculty member at AARHUS University.
3. Faculty member at Emory University.
4. Thorsen allegedly creates fake invoices with...
5. ...the help of a CDC lab section chief.
6. Fake invoices are submitted to AARHUS University for reimbursement.
7. AARHUS reimburses the CDC Credit Union 13 times between 2006 and 2008.
8. The CDC Credit Union accounts receiving the money are private accounts allegedly belonging to Poul Thorsen.
9. Thorsen allegedly buys a house, cars, a motorcycle and other personal items with the money - over \$1 million.
10. His scientific papers are published by mainstream medical journals (*New England Journal of Medicine*, *The Journal of the American Medical Association*, etc.), claiming no link between thimerosal and autism.
11. Dr. Charles B. Nemeroff is a chairman at Emory University.
12. Thorsen contributes to rewriting the definition of autism for the American Psychiatric Association (APA).
13. Dr. Nemeroff is also involved in rewriting the definition of autism for the APA.
14. The APA incorporates autism definitions into DSM-IV (psychiatric guide), favoring chemical medications as treatment.
15. Dr. Charles B. Nemeroff is caught in a financial scandal, then barred from his chairmanship after revelation of secret financial ties to Big Pharma (\$800,000 from GlaxoSmithKline) and barred from submitting grants to the *National Institutes of Health*.
16. Dr. Julie Gerberding is president of the CDC from 2002-2009.
17. Dr. Gerberding is named president of Merck's global vaccine division in 2010.
18. MERCK pays advertising money to top medical journals.
19. AARHUS University submits scientific research to medical journals.

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EXHIBIT 7



# Identification of biological/biochemical marker(s) for preterm delivery

Poul Thorsen<sup>a,d</sup>, Diana E. Schendel<sup>a</sup>, Anjali D. Deshpande<sup>b</sup>, Ida Vogel<sup>e</sup>, Donald J. Dudley<sup>c</sup> and Jørn Olsen<sup>d</sup>

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## Summary

Fetal and neonatal mortality and morbidity rates are strongly associated with gestational age for delivery: the risk for poor outcome increases as gestational age decreases. Attempts to predict preterm delivery (PTD, spontaneous delivery before 37 weeks' gestation) have been largely unsuccessful, and rates of PTD have not improved in recent decades. More recently, the reported associations between infections in pregnancy and PTD suggest preventive initiatives that could be taken.

The overall objective of the current study is to assess whether specific markers of infection (primarily interleukin (IL) 1 $\beta$ , tumour necrosis factor (TNF)  $\alpha$ , IL-6, and IL-10) obtained from maternal blood during pregnancy, alone or in combination with other risk factors for PTD, permit identification of women at risk for spontaneous PTD. To achieve this objective, data are obtained from two Danish prospective cohort studies involving serial collection of maternal blood samples, newborn cord blood samples, and relevant confounders and other risk factors for PTD. The first study consists of a completed Danish regional cohort of 3000 pregnant women enrolled in a study of microbiological causes of PTD, upon which a nested case-control study of PTD in 84 cases and 400 controls has been performed. The second study is a nested case-control study of 675 PTD cases (equally divided into three gestational age categories of 24–29 weeks' gestation, 30–33 weeks' gestation, and 34–36 weeks' gestation) and 675 controls drawn from the ongoing Danish National Birth Cohort study of 100 000 pregnant women enrolled during 1997–2001. The second study will provide the opportunity to refine and retest hypotheses from the first study, as well as to explore new hypotheses. Our preliminary work suggests that a single predictive marker effectively accounting for a large proportion of PTD is unlikely to be found. Rather, a search for multiple markers indicative of the multifactorial aetiology of PTD is likely to be more successful.

Knowledge gained from the proposed studies will be implemented in a third, clinical intervention study against PTD. The first phase of the clinical intervention study will be to establish a risk-assessment model based on the 'best' combination of biological/biochemical measures and other factors associated with PTD in order to identify pregnant women at very high risk of PTD. The second phase will be to apply an intervention model of tailored obstetric care to the very high-risk pregnant women for PTD identified in phase one. The intervention will be carried out against each specific risk factor associated with PTD identified for the individual. The aim is to reduce the risk for PTD attributed to the combination of risk factors included in the clinical intervention study.

## Introduction

In general, low birthweight (LBW, birthweight < 2500 g) and preterm delivery (PTD, delivery before 37 weeks' gestation) are the single factors most strongly associated with neonatal mortality and infant morbidity.<sup>1,2</sup> In the long term, LBW/PTD infants are at higher risk for cognitive, motor, and behavioural developmental problems than are normal birthweight infants delivered at term.<sup>3</sup> Despite the identification of a large number of reproductive, gynaecological, medical, obstetric, and socio-behavioural risk factors for LBW/PTD, attempts to reduce the risk for adverse outcome of pregnancy by a variety of interventions<sup>4</sup> have not reduced the rate of PTD pregnancies in western societies (a persistent rate of 5–12% over the last four decades and twice as high in developing countries<sup>5</sup>).

A large body of evidence suggests that infection of the reproductive tract is an important cause of PTD.<sup>6–11</sup> In specific studies, evidence for upper reproductive tract infection involving the maternal/fetal unit such as histological chorioamnionitis,<sup>12</sup> infected amniotic fluid, and markers of infection detected from the amniotic fluid,<sup>13,14</sup> have been associated with PTD. Several studies have also found associations between infections of the lower reproductive tract, such as *Chlamydia trachomatis* (CT),<sup>15–17</sup> bacterial vaginosis (BV)<sup>18,19</sup> and *Streptococcus agalactiae* (group B streptococcus, GBS),<sup>20</sup> and adverse outcome of pregnancy. *Trichomonas vaginalis*,<sup>21</sup> *Gardnerella vaginalis*,<sup>22</sup> *Escherichia coli*,<sup>23</sup> and anaerobic bacteria<sup>22–24</sup> have also been associated with PTD. Mycoplasmas, primarily *Mycoplasma hominis*, and *Ureaplasma urealyticum*, are still subject to great attention in relation to PTD;<sup>11–25</sup> most investigations indicate that *U. urealyticum* factors in upper reproductive tract infection may lead to an adverse outcome of pregnancy.<sup>26,27</sup> No distinct associations between other aerobic and anaerobic bacteria isolated from the reproductive tract and PTD have been presented consistently, although, *Listeria monocytogenes* can cause intrauterine death and PTD.<sup>28</sup> The strongest evidence for infections in association with LBW/PTD comes from effective intervention trials as carried out by Hauth *et al.*<sup>29</sup> and Morales *et al.*<sup>30</sup>

Pro-inflammatory cytokines (e.g. TNF- $\alpha$ , IL-1 $\beta$ , IL-6) are mediators of inflammation produced by the macrophage/monocyte system in response to, among other things, bacterial products. They are part of, and stimulate further, the cascade of signals that comprises

the inflammatory response to infection. Pro-inflammatory cytokine production is increased among pregnant women with infections in the reproductive tract. IL-1 $\beta$  was elevated in vaginal secretions among BV-positive pregnant women,<sup>31</sup> and elevated levels of IL-6 detected from vaginal secretions were associated with intra-amniotic infections, chorioamnionitis, and IL-6 levels in the amniotic fluid of pregnant women admitted with preterm labour.<sup>32</sup> Pregnant women found culture-positive for bacteria in the amniotic fluid had elevated levels of IL-1 $\beta$ , TNF- $\alpha$  and IL-6 in the amniotic fluid.<sup>33</sup> Furthermore, IL-6 serum levels were elevated among women with preterm prelabour rupture of membranes with clinical or histological chorioamnionitis.<sup>34</sup>

Although initiation and immunomodulation of the primary inflammatory reaction are performed by the pro-inflammatory cytokines, the anti-inflammatory cytokines, such as IL-10,<sup>35</sup> IL-4,<sup>36</sup> and transforming growth factor  $\beta$ <sup>37</sup> species, are produced later in the process and inhibit cytokine synthesis. IL-10 is a key cytokine synthesis inhibitor, yet little is known about IL-10 and infection in the reproductive tract during pregnancy. Greig *et al.*<sup>38</sup> reported elevated amniotic fluid concentrations of IL-10 in women with clinically evident chorioamnionitis, but these findings could not be confirmed by Dudley *et al.*<sup>39</sup> In a small study by Hata *et al.*<sup>40</sup> elevated levels of IL-10 in the umbilical blood were detected among women with chorioamnionitis, but IL-10 could not be detected among women without this condition.

The balance between the activity of pro- and anti-inflammatory cytokines might contribute to the understanding of host susceptibility. An abnormally regulated inflammatory response to a stimulus has been postulated to result in overproduction of cytokines such as IL-1 $\beta$  and TNF- $\alpha$ ,<sup>41</sup> leading to the characteristic clinical spectrum characterising sepsis such as hypotension and organ dysfunction. An imbalance of cytokine function within the fetoplacental unit might also explain an increased susceptibility to infections among a subset of pregnant women resulting in fetal expulsion.<sup>42</sup>

Therefore, we will address the following general hypotheses: (a) multiple aetiological pathways lead to spontaneous PTD; (b) infection in the reproductive tract leads to, and is a primary aetiological factor in, spontaneous PTD; and (c) the aetiological pathways leading to spontaneous PTD are not mutually

exclusive. Specifically, our aims are to determine whether selected pro- and anti-inflammatory cytokine levels (primarily IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-10) measured in maternal serum in pregnancy, alone or in combination with other risk factors for PTD, permit identification of women at risk for spontaneous PTD. To achieve this objective, data will be obtained from two prospective cohort studies involving serial collection of maternal serum samples, and newborn cord blood samples, as well as relevant confounders and other risk factors for PTD. The first study is a pilot study for the latter.

## Methods

### General study design

Our general approach is to conduct two nested case-control studies of PTD based on data collected from two prospective cohort studies: the Odense Cohort Study and the Danish National Birth Cohort. We chose to perform nested case-control studies on the basis of the following considerations. In a nested case-control study, a sample of persons with a given outcome of pregnancy (cases) and a suitable reference group (controls) are identified from the larger prospectively identified cohort. The relationship of an attribute to the pregnancy outcome is examined by comparing the proportions of cases and controls, who have the attribute. This approach is more economical than attempting to examine the relation of interest based on follow-up of the entire cohort. The case-control study design permits multiple analyses, many of which are aptly considered hypothesis-generating. Furthermore, the nested case-control design allows comparisons between selected groups (cases and controls) and the underlying cohort.

### Study populations

#### Odense Cohort Study

The Odense Cohort Study is based upon a regional Odense cohort of 2927 pregnant women prospectively enrolled in a study to investigate microbiological causes of PTD. From the catchment area of the Department of Obstetrics and Gynaecology, Odense University Hospital, Denmark, of approximately 240 000 inhabitants, all pregnant women attending for prenatal care were invited to participate in the study between November 1992 and February 1994. Pregnant women were enrolled at their first antenatal

hospital visit before 24 full weeks' gestation. The inclusion criteria were that the participants be above 18 years of age, able to understand Danish, and plan to deliver at the hospital mentioned. The criteria for exclusion were: incomplete fulfilment of questionnaires, placenta praevia (verified after 30 full gestational weeks), history of severe fetal congenital malformations in previous pregnancy, cervical incompetence treated with cervical cerclage, fetal loss and delivery outside the present hospital.

Among 3596 eligible pregnant women, 3174 (88.3%) agreed to participate in the study. From the enrolled 3174 pregnant women, 247 participants dropped out for the following reasons: delivery at another hospital, incomplete questionnaires, moved from the county, declined to participate further, abortion (induced or spontaneous), stillbirth, delivery at home, and placenta praevia. Thus, the study base consisted of 2927 (81.4%) participants who completed the study, including 81 participants with multiple gestation (Fig. 1).

A pelvic examination including clinical observations was performed on each participant upon enrolment. The examination included taking samples from the cervical os and the vaginal vault to test for aerobic and anaerobic bacteria and other relevant micro-organisms. In addition, a saline wet mount was made for direct microscopy, as well as a urine sample for microbiological examination. Furthermore, samples were taken from the vaginal/cervical secretion and venous blood samples for storage at  $-80^{\circ}\text{C}$ . All participants were asked to fill out three questionnaires: the first at enrolment, a second at 30 weeks' gestation and

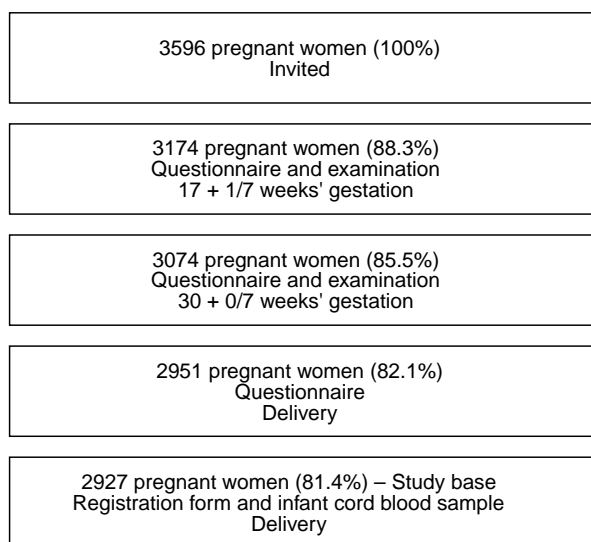
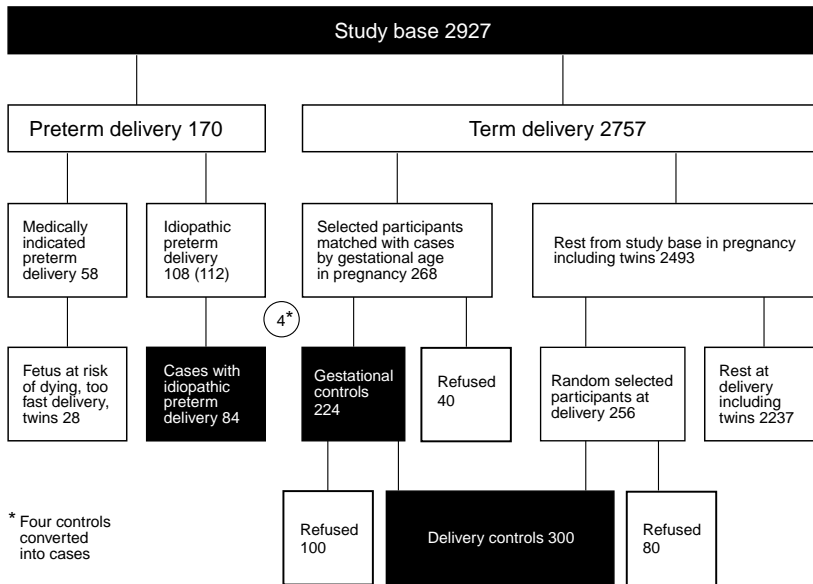


Figure 1. Odense cohort from enrolment until delivery.



**Figure 2.** Design of the Odense Cohort nested case-control study involving 484 singleton pregnant women.

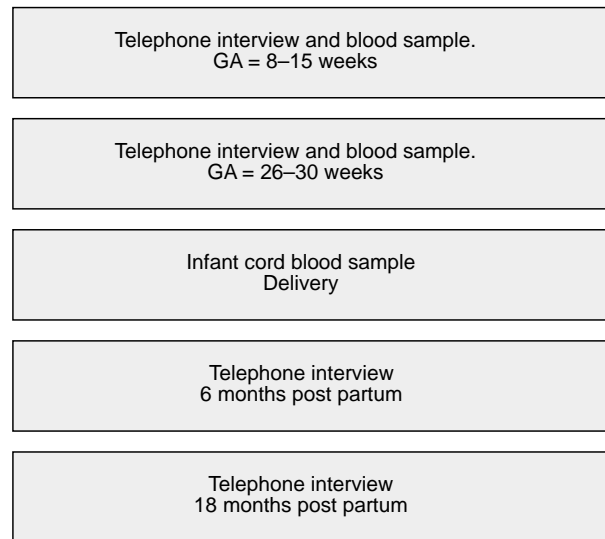
a third at delivery. At delivery, an umbilical cord blood sample was obtained. Shortly after delivery the attending midwife filled out a registration form for the participant.

Estimates of gestational age and estimated date of delivery were calculated from the date of the last menstrual period. Ultrasonographic measurements of the biparietal diameter and the femur length of the fetus at the 18th week of gestation were used to confirm gestational age for 97.5% of the enrolled participants.

A nested case-control study based on the Odense Cohort consists of 484 pregnant women carrying singleton fetuses from the study base representing 84 PTD cases, 224 gestational controls, and 300 delivery controls. The PTD cases and delivery controls had the same examination and sample collection as at enrolment, but when they presented in labour. The gestational controls were individually matched to the PTD cases by gestational age and had the same examination and collection of samples in mid-pregnancy as at enrolment. A subset of 125 from the gestational controls was also included as delivery controls, meaning they were examined three times during pregnancy. Altogether, the Odense Cohort nested case-control study (OCCC) of 484 singleton pregnant women provided 1093 maternal serum samples and 484 infant cord blood samples (Fig. 2).

### The Danish National Birth Cohort

The Danish National Birth Cohort (DNBC) is a study of pregnant women and their offspring in which all pregnant women in Denmark during a 4-year period from 1997 to



**Figure 3.** DNBC data collection from enrolment until post-partum follow-up. GA = gestational age.

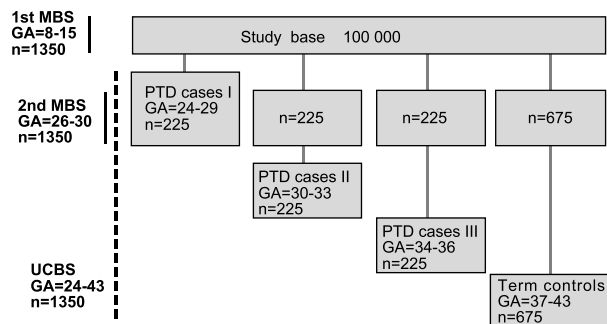
2001 are invited to participate. The overall study aim is to establish a large data bank as the foundation for investigations of the effects of a variety of exposures during pregnancy-on-pregnancy outcome, child development, and ultimately adult health. The overall participation rate is 40% and the aim is to recruit 100 000 women.

A flowchart of the DNBC and data-points to be collected are presented in Fig. 3. In addition to the biological samples and four telephone interviews, information regarding maternal and offspring health can be obtained from existing national registers that cover birth data, malformations and discharge diagnoses from somatic and psychiatric wards. This

information can be extracted and linked to the main study data base by means of the unique Danish personal identification number.

For this study we will perform a nested case-control study of 675 preterm cases (equally divided into three gestational age categories of 225 participants each, delivering at 24–29 weeks', 30–33 weeks', and 34–36 weeks' gestation) and 675 term controls retrospectively identified from the DNBC. Each of the preterm case-groups will be compared with the term control group, as subgroups, and as a total (Fig. 4). The inclusion criteria for preterm cases and controls are: completion of the two prenatal interviews (if delivery is before the second interview before 26–30 weeks' gestation, this interview will be carried out as a postpartum interview immediately after delivery); an ultrasound verified date of delivery; no placenta praevia (verified after 30 weeks' gestation); no cervical incompetence treated with cervical cerclage; no major fetal anomalies; singleton pregnancies; initiation of spontaneous delivery either by rupture of membranes or by labour; and complete blood samples (one umbilical cord blood sample, two maternal blood samples for controls and for preterm cases delivering after 30 weeks' gestation, and one maternal blood sample for preterm cases delivering at 24–29 weeks' gestation). Preterm cases within each gestational age category will be selected consecutively and participants for the control group will be randomly selected from the study base fulfilling the inclusion criteria.

Thus, the DNBC nested case-control study (DNBCCC) will include three times as many preterm cases and controls as the OCCC, yielding approximately 2700 maternal blood samples and 1350 umbilical cord blood samples obtained from 1350 participants.



**Figure 4.** Design of the DNBC nested case-control study involving 1350 singleton pregnant women providing around 4050 samples. GA, gestational age in weeks; MBS, maternal blood sample; UCBS, umbilical cord blood sample; PTD, preterm delivery.

## Selection of biological/biochemical markers and compartment

### Biological/biochemical markers

The cytokines IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$  were chosen for this investigation on the basis of:

1. their association with infectious processes/immunological cascade;
2. indications of a disturbed balance between pro-inflammatory and anti-inflammatory cytokines as a cause of increased susceptibility to PTD among a subset of pregnant women;
3. their association with PTD;
4. their association with other markers (discussed below); and
5. preliminary results from the OCCC on IL-6 detected from vaginal/cervical secretions and maternal serum.

Biochemical/biological markers with the strongest association with PTD in the OCCC, alone or in combination with other relevant factors, or in subgroups of women who deliver preterm, will be selected for confirmation in the DNBCCC. Also, relevant factors showing trends in OCCC will be explored in the DNBCCC for associations with PTD. However, an important practical determinant for selecting the final arsenal of markers to be measured in the DNBCCC is the amount of tissue required to perform the laboratory measurements in doublets and with sensitive results.

### Compartment

Samples from the vaginal/cervical compartment require a pelvic examination, which may have adverse health consequences, and may also present difficulties in obtaining valid measurements for detection of concentration, and bias from sampling, e.g. because of bleeding. Although some previous studies have focused upon amniotic fluid, sampling amniotic fluid requires amniocentesis, which is impractical from a population-based perspective and increases the risk of spontaneous abortion. In comparison with the amniotic cavity, less attention has been paid to sampling maternal serum. To collect serum samples is practical for population-based applications, including obtaining serial measurements throughout pregnancy. Sampling cord blood is the least invasive approach, although it is impractical if the goal is to predict PTD. Nevertheless, it has the potential to confirm fetal exposure to elevated levels of cytokines.

Thus, given that (a) our goal is to identify predictive markers for impending PTD as early in pregnancy as possible to consider preventive actions; (b) we regard the process initiating labour before term to be generalised involving steroid and peptide hormones, cytokines, and oxytocic factors, among others; and (c) ideally, measurement of the identified factor(s) should be acquired conveniently without risks to the mother or to the fetus and to be reproducible across populations, maternal blood was selected as the compartment for detection of markers for PTD. Umbilical cord blood is a confirmatory compartment.

### Other data collection

Data on sociodemographic and other risk factors for PTD will be obtained from data collected as part of the Odense Cohort Study and the DNBC.

In the Odense Cohort Study all participants were required to complete self-administered questionnaires on three occasions during pregnancy:

Questionnaire I: primarily concerns previous and current gynaecological/obstetric conditions and previous and current medical/surgical conditions and was completed by the participant just before the first antenatal visit. All responses from this questionnaire were reviewed in the participant's presence so she could provide any additional information.

Questionnaire II: primarily concerns sociodemographic factors and was completed by the participant just before the routine visit at 30 weeks' gestation.

Questionnaire III: primarily concerns current urogenital and obstetric conditions and was completed just before delivery and returned by the participant.

Finally, shortly after delivery the midwife filled out a registration form concerning the course of delivery and complications in pregnancy and at delivery.

Before the study was started the three questionnaires were evaluated and modified from a small pilot study including 160 randomly selected pregnant women attending for prenatal care. Reproductive history data from the questionnaires (primarily questionnaire I) were consistent with the medical records in 97.6% of the cases. Midwives were trained in filling out the registration form before the study was initiated.

The DNBC includes telephone interviews performed by qualified staff with special training in medicine and interview techniques. Data from the four telephone interviews are entered directly into personal computers. The four interviews concern the following topics:

Interview 1 (12 weeks' gestation, 10–15 min): previous and current gynaecological, obstetric, medical, and surgical problems, drug consumption including exposure to smoke and intake of alcohol, level of physical activity, education, work, information about husband/father, and housing.

Interview 2 (30 weeks' gestation, 10–15 min): current obstetric and medical problems, worries and stress, work, intake of vitamins, drugs, alcohol, exposure to smoke and resting.

Interview 3 (6 month postpartum, 15–20 min, regarding the child): serious physical or developmental disabilities including confirmed cerebral damage, generally delayed development, problems with hearing, problems with sight, motor problems, and more specific questions on physical skills/motor development/perception of surroundings.

Interview 4 (18 months postpartum, 15–20 min, regarding the child): same format as Interview 3, but corresponding to the age of 18 months.

### Study power

The following calculations were performed on the basis of data from the literature to achieve the most cost-effective studies. We used two-tailed power estimates at alpha level of 5%, and used odds ratios as estimates of relative risks.

In the OCCC, separate power calculations were based on the whole control group ( $n=400$ ), on the gestational control group ( $n=224$ ), and on the delivery control group ( $n=300$ ). For the whole control group, there is 66% power to demonstrate a relative risk of 2.5 with exposures (e.g. elevated TNF- $\alpha$ ) of 10% among controls; for a relative risk of 3.0 there is 87% power. For the gestational control group, there is 60% power to identify a relative risk of 2.5 for exposures at 10% prevalence among controls; for a relative risk of 3.0 there is 82% power. For the delivery control group, equivalent figures are 63% power and 85% power.

In the DNBCCC, three times as many preterm cases and controls as in the OCCC are selected to increase study power and the precision of the measures of association and to allow analyses of trends found in the OCCC. With 225 cases and 675 controls, 60% power is achieved at an exposure of 2.5% among controls and a relative risk of 2.5; 80% power is achieved at 2.5% exposure and a relative risk of 3.0. With 675 cases and 675 controls, 60% power is achieved at an exposure of 2.5% among controls and a

relative risk of 2.0; 80% power is achieved at 3.75% exposure and a relative risk of 2.0.

### Laboratory methods

#### Sampling and laboratory methods for the OCCC

Maternal samples were obtained from the participants at enrolment (mean  $\pm$  SD: 16.9  $\pm$  2.9 weeks for PTD cases vs. 16.4  $\pm$  2.6 weeks for controls), in mid-pregnancy (mean  $\pm$  SD: 34.2  $\pm$  2.8 weeks for PTD cases vs. 32.5  $\pm$  2.5 weeks for controls), and at delivery (mean  $\pm$  SD: 34.2  $\pm$  2.8 weeks for PTD cases vs. 40.3  $\pm$  1.3 weeks for controls). Umbilical cord blood samples were obtained at delivery.

Methods for microbiological cultures and tests including related sampling from the genital tract have been published.<sup>43</sup>

Additional vaginal/cervical samples were collected from the cervical os and the posterior fornix after the vault of the vagina had been exposed to a sterile non-lubricated vaginal speculum. The samples were obtained with sterile, cotton-tipped wooden swabs and were inoculated directly into 1 mL of sodium chloride solution (0.9%) containing 2% sterile calfserum (Life Technologies Inc., Gaithersburg, MD, USA). Immediately after collection, the sample was frozen to  $-80^{\circ}\text{C}$  until thawed for testing.

Maternal samples of venous blood (7 mL) were obtained in dry, sterile tubes, cooled at room temperature, centrifuged and aliquoted within 2 h from collection. The samples are stored at  $-80^{\circ}\text{C}$ .

Umbilical cord blood samples (5 mL) were obtained in dry, sterile tubes, cooled at room temperature for 1 h, cooled at  $4^{\circ}\text{C}$  temperature. Centrifuging and aliquoting were performed within 12 h from collection. The samples are stored at  $-80^{\circ}\text{C}$ .

When the first measurement on the stored samples was to take place, the remainder of the aliquot was divided into tubes of 125  $\mu\text{L}$  each and then stored at  $-80^{\circ}\text{C}$ , so that the samples were not thawed more than twice before testing.

All laboratory measurements performed on the vaginal/cervical samples, the maternal serum, and the fetal serum are displayed in Table 1.

The laboratory analyses for IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IL-10 from maternal and fetal serum were performed at the Reproductive Sciences Laboratory, University of Utah School of Medicine, Salt Lake City, UT, USA, using commercially available Quantikine kits from

**Table 1.** Biological and biochemical markers completed for the Odense cohort nested case-control study.  $n = 484$

Biomarkers	Vaginal fluid <sup>a</sup>	Maternal blood <sup>a</sup>	Fetal blood
Unspecific heat shock protein	X	X (enrolment)	
<i>Chlamydia trachomatis</i> -specific heat shock protein		X	
Prolidase	X		
Sialidase	X		
Anti <i>Gardnerella vaginalis</i> haemolysin IgA	X		
Insulin-like growth factor binding protein I	X		
Defensin	X		
Lactoferrin	X		
Albumen	X		
Fetal antigen 1		X	X
C-reactive protein		X	
Ferritin		X	
Relaxin		X	
Estriol		X	
Human chorion gonadotropin		X (enrolment)	
Alpha feto-protein		X (enrolment)	
Corticotropin releasing hormone (CRH) binding protein		X	X
Free CRH		X	X
Bound CRH		X	X
Total CRH		X	X
Cortisol		X	X
Mannan binding lectin		X	X
Neopterin		X	
Tumour necrosis factor $\alpha$		X	X
Interleukin 1 $\beta$		X	X
Interleukin 6	X	X	X
Interleukin 8	X		
Interleukin 10		X	

<sup>a</sup>Two and three times during pregnancy.

In addition to the tests presented, classic microbiological measurements from the urogenital tract such as bacterial vaginosis were performed on the Odense cohort (including the nested case-control study).<sup>43</sup> Furthermore, the following serological analyses are completed on the Odense cohort (including the nested case-control study): *Chlamydia trachomatis* serology: Complement fixation test, Micro Immuno-fluorescence test for IgG and IgM. Viral serology: *Human Parvovirus B19*,<sup>77</sup> *Herpes simplex virus* type I and II, cytomegalovirus.

R & D Systems (Minneapolis, MN). For each cytokine, the high sensitivity approach was employed. The assay methods are as follows:

1. Reagent preparation: Each assay uses a quantitative sandwich immunoassay: (a) all reagents are brought to room temperature before use; (b) wash buffer: 20 mL of wash buffer concentrate is diluted to 500 mL of wash buffer with distilled water; (c) substrate solution: colour reagents A and B are mixed in equal volumes just before use; (d) standards: cytokine standards are reconstituted with 5 mL of calibrator diluent RD6C (for serum).

- (i) IL-1 $\beta$ : stock solution of 8 pg/mL.
- (ii) TNF- $\alpha$ : stock solution of 32 pg/mL.
- (iii) IL-6: stock solution of 10 pg/mL.
- (iv) IL-10: stock solution of 25 pg/mL.

2. Assay procedure (bench-top approach): (a) assay diluent RD1C, 50  $\mu$ L, is added to each well of the prepared 96-well microtitre plate (previously coated with capture antibody for each specific cytokine to be tested); (b) 200  $\mu$ L of sample or standard is then added to each well (eight different standards will be used to create the standard curve and will be done in duplicate. Samples will also be assayed in duplicate, such that 40 samples will be assayed on each plate); (c) samples are incubated with capture antibody for 14–20 h at 2–8°C; (d) each well is aspirated, and rinsed four times with wash buffer; (e) detection antibody, at an appropriate concentration, is then added to each well (200  $\mu$ L volume) and incubated for 3 h at room temperature; (f) each well is aspirated, and rinsed four times with wash buffer; (g) to each well is added 50  $\mu$ L of substrate solution and incubated for 20 min at room temperature; (h) 50  $\mu$ L of amplifying solution is added to each well for 30 min; (i) 50  $\mu$ L of stop solution is added to each well and the optical density at 450 nm is determined on a microplate reader within 30 min of final development.

### Sampling and laboratory methods for the DNBCCC

Maternal samples are collected from the participants during antenatal visits with their general practitioner as shown in Fig. 3. Umbilical cord blood samples are collected at delivery.

Maternal samples of venous blood (7 mL) are obtained in sterile tubes containing EDTA, cooled at room temperature, cooled at 4°C temperature until centrifugation and aliquoting performed within 36 h from collection. The samples are stored at –80°C.

Umbilical cord blood samples (5 mL) are obtained in sterile tubes containing EDTA, cooled at room temperature, cooled at 4°C until centrifugation and

aliquoting performed within 36 h from collection. The samples are stored at –80°C.

All samples will be thawed once for aliquoting into adequate volumes for testing.

Conventional enzyme immunoassay and radioimmunoassay methods for the DNBCCC laboratory analyses will be considered together with more advanced techniques with the ability to perform multiple measures on smaller amounts of material. The optimum method for the quantity of sample available for the study will be selected.

### Analytical strategy and statistical analyses

Overall, the goal of these analyses is to identify early predictors of PTD using conventional statistical tools as well as more advanced statistics (outlined below). We believe that many different pathways may converge upon a final, common route involving the immune system that results in parturition. The approach outlined below is applicable for other possible PTD predictors, but is exemplified here for cytokines.

#### Analysis aim 1

To describe the natural history of IL-1 $\beta$ , IL-6, IL-10 and TNF- $\alpha$  as measured in maternal serum during the course of term pregnancy and delivery.

Some assumptions that will be tested before proceeding with more complex analyses are that we expect the serum concentration of each cytokine to vary with gestational age and that the distribution of each cytokine at each measurement point will be skewed (not normally distributed).

Absolute concentrations at each measurement point and percentage change in cytokine concentration over time will be determined. The distribution of cytokine measurements at each measurement point will be described using the median value and range for each cytokine. Graphical methods will be included to describe the cytokine pattern/distribution over time. For the OCCC, the rate of change in cytokine concentration over time will also be determined for each cytokine using mixed-effects regression modelling with both fixed and random effects.<sup>43,44</sup>

Mixed-effects regression will be used to examine changes in cytokine concentration over time, and to identify factors related to that change. The mixed-effects models will allow estimation of average cytokine concentration curves ('growth curves') and estimation



of each subject's cytokine change over time, which can then be compared with the group average. The models will include both fixed and random effects. Some of the fixed effects to be considered will be gestational age, maternal age at enrolment, presence of a serious medical disease at enrolment, and enrolment levels of each of the other cytokines under study. The only random effect to be considered will be a random intercept, which describes the degree to which an individual's mean value differs from the population average. We assume that the overall pattern is similar across individuals, so a random slope is not specified. Standard methods for determining the final model and assessing model fit will be used.

### Analysis aim 2

To determine whether a difference exists in the level of each cytokine between cases and controls at each measurement point during pregnancy and at delivery.

Descriptive statistics (medians and ranges) for each cytokine at each measurement point will be done for the case group and each control group separately as described above.

To determine whether cytokine concentrations differ between cases and controls, we will compare their distributions at the different measurement points using the Wilcoxon rank sum test for non-parametric data.

- Comparison between cases and all controls of samples taken at enrolment will assess differences early in pregnancy.
- For the OCC, comparison between cases at delivery and gestational controls of samples taken at the time of case delivery/matching will assess differences resulting from delivery effects, controlling for gestational age.
- For the OCC, comparison between cases and controls of samples taken at delivery will assess differences at delivery/older gestational age.

To assess the relation between the four cytokines under investigation, IL-1 $\beta$ , IL-6, IL-10 and TNF- $\alpha$ , we will determine Spearman correlations between cytokine markers in cases separately from controls.

### Analysis aim 3

To determine the association between any of the cytokine markers measured at enrolment and PTD.

Results from the previous two analyses will direct these analyses. Only exposures that show significant

differences between cases and controls in the univariate analyses will be included in multivariate analyses. The correlation analyses will determine how closely related the markers are and whether there is colinearity between markers.

Unconditional logistic regression analysis will be used to account for multiple exposures and covariates in assessing the relation between cytokine concentrations at enrolment and PTD. The outcome under study is defined as gestational age at delivery, which is a dichotomous variable (e.g. < 37 weeks' gestation compared with  $\geq$  37 weeks' gestation). The exposures to be studied are the concentrations of IL-1 $\beta$ , IL-6, IL-10 and TNF- $\alpha$  at enrolment. These concentrations will be assessed as categorical variables, defined as empirical quartiles based on the distribution of each immune marker in the control group. Effect modification and confounding will be assessed using stratified analyses. Covariates that are major risk factors for PTD will be included as a priori confounders and will be retained in the model regardless of statistical significance. Additionally, other covariates (e.g. infection variables, demographic and behavioural factors) will be assessed for their potentials as confounders by determining their association with the exposure in the study controls and their association with the outcome as described in the literature. Regression diagnostics and goodness of fit tests will be used to assess the fit of the final predictive model against the data.

### Analysis aim 4

The final aim of this analysis is to determine the predictive ability of each immune marker and our final logistic models (from Analysis aim 3). This will be done using receiver-operator characteristic (ROC) curves to compare several cut-points for each relevant cytokine in order to find the level(s) that best discriminates between cases and controls based on sensitivity and specificity. This method will also be used to compare the predictive ability of the best-fitting models developed in the logistic analysis.

Because we are interested in the interactions between the cytokines and the effect of these interactions on the outcome, recursive partitioning will be used as an alternative technique to create decision rules, which can be used to predict PTD. Recursive partitioning is considered to be more sensitive to discriminating interactions between variables than logistic regression, but unlike logistic regression, this

method will not give us information about the effect of individual markers on preterm birth but will instead identify high-risk groups. Also, recursive partitioning will allow us to identify cut-off values for each marker (that concentration that provides the best discrimination between cases and controls in the high-risk groups). Classification trees derived by recursive partitioning also will provide measures of sensitivity and specificity for discriminating between cases and controls for each of the markers.

## Discussion

### *Cytokines and other biochemical factors in a multifactorial model of PTD*

Cytokines are not only associated with most of the factors involved in the infectious process, but may also be associated with many of the biochemical factors associated with adverse outcome of pregnancy, exemplified below.

Infections of the lower reproductive tract such as BV and CT are associated with elevated levels of local IL-1 $\beta$  and IL-6.<sup>31,45,46</sup> A general systemic host response has not been investigated in respect to cytokines for infection of the lower reproductive tract by BV or CT.

Local markers for infection of the lower reproductive tract have also been associated with both adverse outcome of pregnancy and cytokine production. Heat shock proteins (HSP) are cellular stress proteins synthesised in both eukaryotic organisms and bacteria in response to environmental stress. They perform functions essential to cell survival under these conditions. HSP synthesis is considerably increased in cells exposed to various infectious agents.<sup>47</sup> Unspecific HSP also increases cytokine production by macrophages.<sup>48</sup> Likewise, defensin, a marker for neutrophil activation, is activated by infection of the reproductive tract and most likely capable of inducing action against infectious agents<sup>49</sup> by modulating the level of IL-6 among others;<sup>50</sup> defensin has not yet been explored for associations with adverse outcome of pregnancy. Another marker for infection of the lower reproductive tract is lactoferrin, also a neutrophil product, which is modulated by TNF- $\alpha$  (tested on peripheral blood neutrophils)<sup>49</sup> and associated with PTD.<sup>51,52</sup>

Systemic factors associated with adverse outcome of pregnancy, mostly representing the maternal entity, such as relaxin,<sup>53</sup> have also been associated with adverse outcome of pregnancy. Petersen *et al.*<sup>53</sup> found

a 40% increase in serum relaxin at 30 weeks' gestation among pregnant women delivering preterm compared with controls. To our knowledge, it has only been speculated that relaxin is related to cytokine production<sup>6</sup> or indirectly associated with cytokine actions.<sup>54</sup> Another and potent factor, corticotropin releasing hormone, has been associated with term and preterm parturition<sup>55</sup> and cytokine production.<sup>56</sup> IL-6 stimulates the hypothalamic-pituitary-adrenal axis, which can be measured as elevated plasma cortisol, among other effects. A study by Mazor *et al.*<sup>57</sup> found elevated plasma cortisol associated with unsuccessful tocolytic treatment of PTD. Ferritin, an important factor in regulation of iron metabolism, is stimulated by IL-6<sup>58</sup> and associated with PTD, particularly when detected in the second trimester.<sup>59</sup> A marker for monocyte activation, neopterin, increases after TNF- $\alpha$  injections<sup>60</sup> and might be associated with PTD, as reported in a study by Oleszczuk *et al.*<sup>61</sup>

Factors mostly representing the fetomaternal unit such as human chorionic gonadotrophin (HCG)<sup>62</sup> and alpha fetoprotein (AFP)<sup>63</sup> are associated with adverse outcome of pregnancy and might in combination be strong predictors of PTD.<sup>64</sup> AFP downregulates production of TNF- $\alpha$ ,<sup>65</sup> which on the other hand induces production of HCG.<sup>66</sup> Salivary oestriol was found associated with PTD, especially if the measurement was in early pregnancy.<sup>67</sup> This hormone is involved in regulation of cytokine production, particularly during endotoxin challenge.<sup>68</sup>

Inherited decreased host response or inherited increased host susceptibility seem also to be a potent factor in the infectious genesis of PTD. Mannan binding lectin (MBL) is an inherited factor representing a third pathway of the complement system and is associated with susceptibility to infections.<sup>69</sup> MBL has been associated with recurrent miscarriage possibly from cytokine imbalance within the fetoplacental unit.<sup>42</sup>

Within the amniotic compartment (amniotic fluid), the cytokine network has been explored in detail in respect to adverse outcome of pregnancy and the association is evidently positive.<sup>70-74</sup>

In summary, the pathway to PTD from infection of the reproductive tract (including intrauterine infection) seems to be facilitated through the cytokine network either directly or indirectly.<sup>6,7,10,11,33,75,76</sup> However, understanding of the role of the cytokine network as a potential predictive factor for PTD requires consideration of possible interactions with other risk factors.

### Strengths and limitations of the OCCC and the DNBCCC

The strengths of the OCCC for this study are: (a) population-based; (b) high rate of compliance (81%) and high quality of data (valid and precise); (c) complete prenatal and outcome of pregnancy information; (d) complete measurements on infections from both vaginal/cervical tests and tests on maternal serum; (e) serial maternal serum samples and infant cord blood samples on which a large number of tests on potential markers for PTD have been made (Table 1); and (f) an opportunity to investigate the relation among multiple markers of PTD, as well as for creating 'normal' values during pregnancy based on the serial measurements. Further possibilities arise for elucidating pathogenetic pathways.

The strengths of the DNBCCC are: (a) population-based; (b) high data-quality; (c) complete prenatal and outcome of pregnancy information; (d) large sample size and high study power; (e) collection of two maternal blood samples (at 8–15 and 26–30 weeks' gestation) and an umbilical cord blood sample at delivery; (f) ability to confirm results found in the OCCC; (g) possibility of performing follow-up of mothers, fathers, and developmental status of children by linkage to existing interviews and complete disease registers; and (h) possibility of exploring genetic markers associated with biological predictors identified in the OCCC and DNBCCC.

Limitations for the study include: (a) limited power to detect associations in subgroups of women delivering preterm (i.e. primigravidae or women with a specific infection or behavioural risk factor); (b) lack of confirmation of intrauterine infection from lack of amniotic fluid or placental cultures; (c) limited generalisability because the study sample reflects the conditions in an extremely homogeneous Caucasian population, meaning that any comparisons with more diverse populations and other ethnicities has to be evaluated carefully.

### Implementation of results into a tailored intervention model

As the pathways leading to PTD are multiple and multifactorial, and because many aetiological factors are connected and interactive, e.g. smoking and reduced resistance to infections, we propose an intervention model individualised among pregnant women with high risk of delivering preterm i.e. a tailored intervention.

Thus, knowledge gained from the proposed studies will be implemented in a third, clinical intervention study against PTD. The first phase of the clinical intervention study will be the establishment of a risk-assessment model based on the 'optimal' combination of biological/biochemical measures and other factors associated with PTD to identify a limited group of pregnant women at very high risk for PTD early in the second trimester. The second phase will be to apply a model of tailored intervention to these very high-risk pregnant women identified in phase one. The intervention will be based upon specific risk factors associated with PTD determined for the individual. This will be done in a clinical trial in which participants will be randomised to either tailored intervention (e.g. smoking cessation for a woman who smokes and an antibiotics scheme to a second woman with vaginal infection) or no intervention. The outcomes of interest include PTD and indicators of perinatal morbidity and mortality. The goal will be to reduce the risk for PTD attributed to the combination of risk factors included in the clinical intervention study.

### Acknowledgements

This research was supported financially by the Danish Health Insurance Foundation, the Institute of Clinical Research, University of Odense, the Foundation of Reproductive Biology, Odense University Hospital, the National Fund for Research and Development, the Danish Ministry of Health, the Medical Scientific Foundation for Copenhagen, Faroe Islands & Greenland, Merchant Sven Hansen and Mrs Ina Hansens Foundation, Director Jacob Madsen and Mrs Olga Madsens Foundation and the Nordic Union of Obstetricians and Gynaecologists Foundation, Odense University Hospital, Denmark. The activities of The Danish Epidemiology Science Centre are financed by a grant from The Danish National Research Foundation. Further, the study was supported by a grant from March of Dimes Birth Defects Foundation, New York, and supported under a cooperative agreement from the Centers for Disease Control and Prevention, Atlanta, through the Association of Teachers of Preventive Medicine, Washington DC, USA.

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EXHIBIT 8

**Poul Thorsen – Diana Schendel Co-Authorships  
Relationship Continues after Indictment**

1: Carlo WA, McDonald SA, Tyson JE, Stoll BJ, Ehrenkranz RA, Shankaran S, Goldberg RN, Das A, Schendel D, Thorsen P, Skogstrand K, Hougaard DM, Oh W, Lupton AR, Duara S, Fanaroff AA, Donovan EF, Korones SB, Stevenson DK, Papile LA, Finer NN, O'Shea TM, Poindexter BB, Wright LL, Ambalavanan N, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Cytokines and neurodevelopmental outcomes in extremely low birth weight infants. *J Pediatr*. 2011 Dec;159(6):919-25.e3. Epub 2011 Jul 27. PubMed PMID: 21798559; PubMed Central PMCID: PMC3215787.

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**Poul Thorsen – Diana Schendel Co-Authorships  
Relationship Continues after Indictment**

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**Poul Thorsen – Diana Schendel Co-Authorships  
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EXHIBIT 9

## APA DSM5 Work Group Member Disclosure Report

Name : Poul Thorsen, MD, PhD  
Job Title : Adjunct Associate Professor  
Address : 1505 Race Street, Bellet Building, 11th Floor  
Philadelphia PA 19102-1192  
Role : **Member**  
Date : **1/22/2010**

### WorkGroup:

Neurodevelopmental

### Biographical Sketch

Biographical Sketch:

Poul Thorsen, M.D., Ph.D.

Member, Neurodevelopmental Disorders Work Group

Adjunct Associate Professor, Department of Epidemiology and Biostatistics, School of Public Health, Drexel University, Philadelphia, PA, USA

Dr. Thorsen has since his first project, initiated in 1987 as a medical doctoral student, managed a considerable number of studies on autism, national as well as international. Dr. Thorsen finished his training as MD 1989 and during a period of 3 years thereafter completed his internship. His research career was initiated in 1992 and he worked on the Danish National Birth Cohort first time 1996; was visiting scientist at the Centers for Disease Control and Prevention, Atlanta, GA, USA (CDC) 1997-2000; was Associate Professor, Department of Epidemiology, School of Public Health, University of Aarhus, Denmark, 2000-2008; Research Professor at Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, USA, 2008-2009, and associate at the Department of Epidemiology, Johns Hopkins University, Baltimore, USA, since 1999. Further, during the period 1998-2005 Dr. Thorsen has been a March of Dimes, PERI grantee, and for the period 1999-2008 Dr. Thorsen was appointed principal investigator on the "Epidemiologic studies of reproductive and developmental outcome – Denmark" from CDC. Dr. Thorsen is author or co-author of more than 90 scientific articles and book chapters. During the period 2000-2008 Dr. Thorsen established the research group, "North Atlantic Neuro-epidemiology Alliances" (NANEA) originally initiated through research on Cerebral Palsy in 1999-2000. NANEA's main research areas are: a) autism, b) cerebral palsy c) neuropsychological development, d) preterm birth, e) Down syndrome, and f) Hearing loss. At present, the research network comprises more than 30 persons, who are affiliated with the above areas of research (a-f).

The table below represents the reported disclosures of significant interests and affiliations for the past full calendar year and the current year to date for Poul Thorsen, MD, PhD.

Dr. Poul Thorsen, MD, PhD has agreed that, from the time of approval through the publication of DSM-V, projected in 2012, (his/her) aggregate annual income derived from industry sources (excluding unrestricted research grants) will not exceed \$10,000 in any calendar year.

<b>Commercial or Other Organization</b>	<b>Year(s)</b>	<b>Relationship</b>	<b>Key(s)</b>
Ludvig og Sara Elsass Foundation	2005 - Present	Self	Grant
Danish Medical Research Council	2006 - Present	Self	Grant

The table below represents the reported disclosures of uncompensated leadership positions with Non-Profit or Advocacy Organizations that may have a direct or indirect interest in psychiatric diagnosis, treatment, or the DSM-V for the three years prior to appointment and the current year to date for Poul Thorsen, MD, PhD.

<b>Non-Profit or Advocacy Organization</b>	<b>Year(s)</b>	<b>Relationship</b>	<b>Role</b>
None			

EXHIBIT 10



[Home](#) [About DSM-5](#) [Meet Us](#) [Research Background](#) [General Resources](#) [Proposed Revisions](#) [Newsroom](#)

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## Autism and Other Pervasive Developmental Disorders Conference (February 3-5, 2008)

Prepared by Michael B. First, M.D., DSM Consultant to the American Psychiatric Institute for Research and Education (APIRE), a subsidiary of the American Psychiatric Association

The APA, in collaboration with the WHO, NIH, and the M.I.N.D. Institute at the University of California, Davis, convened a diagnosis-related research planning conference focusing on autism and other pervasive developmental disorders at the M.I. N.D. Institute in Sacramento California, on February 3-5, 2008. The conference was the last in a series of NIH-funded conferences on "The Future of Psychiatric Diagnosis: Refining the Research Agenda" that is administered by APA's American Psychiatric Institute for Research and Education (APIRE). The conference co-chairs were Susan Swedo, M.D., National Institute of Mental Health (Bethesda, MD), Poul Thorsen, M.D., Ph.D., University of Aarhus (Aarhus, Denmark), and Daniel Pine, M.D., National Institute of Mental Health (Bethesda, MD.) Twenty six invited scientists from around the world participated.

### Related Links

Susan Swedo, M.D. (Bethesda, MD), co-chair of the conference and chair of the *DSM-V* Autism Work Group, began by providing an overview of the plans for the *DSM-V* work group. The job of the work group is to identify criteria that will be more accurate and precise and to determine what data are needed to recommend a change in the criteria. Given that the work group does not have the resources to collect new data; recommendations will have to be based on a review of the literature and on secondary analyses of existing data. She emphasized that all changes must be warranted by data and by experience in the field and warned against just tinkering with the diagnostic criteria. Proposed new criteria for autism will need to be reliable, valid, and developmentally sensitive and will need to be tested out in field trials. She noted that the audience for the *DSM* is diverse: primary care clinicians are the main users, so criteria must be clinically useful and manageable, given that clinicians often have only five minutes to do their evaluations. The agenda of the conference is divided into a series of nine panels, each one focusing on a question that was raised during the first meeting of the *DSM-V* Autism Work Group.

The first panel addressed the question what are the core symptom domains in autism? Three alternatives have been proposed: social deficits only (leading to communication deficits and repetitive/fixated behavior), social and communication deficits (but not repetitive behaviors/fixated interests), or all three symptom domains (i.e., social deficits, communication deficits, and repetitive behaviors/fixated interests), as currently defined in *DSM-IV*. In her introduction to the panel, Amy Wetherby, Ph.D., (Tallahassee, Florida) noted that currently the core symptoms of autism are divided into three domains: impairment in social interaction (e.g., impairment in the use of nonverbal behavior; lack of spontaneous sharing; lack of social/emotional reciprocity; failure to develop peer relationships), impairment in communication (e.g., delay in or lack of development of spoken language and gestures; impairment in the ability to initiate or maintain conversation; repetitive and idiosyncratic use of language; lack of pretend play), and repetitive behaviors and fixated interests (e.g., preoccupation with restricted patterns of interest; inflexible adherence to routines; repetitive movements; preoccupation with parts of objects). A prospective study of the general population which looked at 29 features to see which features at age 2 predicted the later development of an Autistic Spectrum Disorder (ASD) found nine features from the three domains, supporting the notion of a triad of domains. Looking at the ability of these features to distinguish between ASD, other developmental disorders, and typical development both early and late during the second year, repetitive movements of objects (e.g., swiping, rubbing, squeezing objects, lining up objects, collecting objects) were better able to distinguish between ASD and developmental disorder both early and late during the second year of life than were repetitive movements of the body (e.g., flapping arms or hands, rubbing, tapping, or pressing body parts, stiffening fingers, hands, or arms) or social communication problems, which can only distinguish between these groups later during the second year, suggesting that there may be separate strands underpinning ASD early on which become intertwined by late in the second year. In her presentation, Catherine Lord, Ph.D., (Ann Arbor, MI) recommended caution when doing factor analyses on ASD data sets, given that subject characteristics and instrument characteristics affect results. All studies have found considerable correlations between factors (with correlations between 0.37- 0.66, at least for restricted, repetitive behaviors) and have required oblique factors, but that the number of factors has differed greatly across studies. Most of the studies have suggested that social items and non-verbal items are hard to separate but, on the whole, non-verbal communication items are the elements that go together to create social deficits. Dr. Lord proposed that the diagnostic criteria for autism include social communication deficits and restricted, repetitive behaviors and that chronological age, current expressive language level, nonverbal IQ, and resulting impairment also be taken into account. John Constantino, M.D., (St. Louis, MO), in his presentation, noted that, 1) autism represents the severe end of a continuum of inherited social deficiencies that occur in nature and it is arbitrary where to draw the line between affected and normal states.; 2) there are no data that support Asperger's disorder breeding true; familial idiopathic PDDs share genetic origins; for example, in a Danish epidemiological sibling study, both autism and Asperger's disorder increase the

risk of autism in siblings (although the risk is higher for probands with autism); 3) *DSM-IV* criterion domains for autism are NOT empirically-derivable by factor, cluster, or latent class analyses, suggesting a unitary underlying factor structure; 4) that although ADHD and PDD share some secondary symptoms, they are inherited largely independently, can co-occur, have been shown to respond independently to some of the same treatments and therefore should be allowed to be diagnosed simultaneously (i.e. NOT mutually exclusive for assignment of diagnosis); and 5) an important goal for *DSM-V* is to develop norms that provide the structure for a system of dimensional characterization of developmental psychopathology (for example, how much deficiency in impulse control should be expected for a child with an IQ of 75?). Finally, Francesca G. Happé, Ph.D., (London, UK), presented data regarding whether the familiar triad of impairments in autism (i.e., social impairments, communication impairments, and restricted repetitive behavior and interests) are all due to a single underlying cause or whether they are influenced by separate causes. In studies of a population-based sample of twins (at ages 7, 8, and 10), correlations between trait measures of the three triad areas ranged from 0.3 to 0.4. In addition, cross-twin cross-trait correlations suggested that at least half the genes acting on these (highly heritable) traits act specifically on one part of the triad. While the data on children with extreme (impaired) scores in each domain do suggest that the three triad impairments cluster above chance, there are large numbers of children with parent-reported impairments in just one triad area. The results from these studies indicate that aspects of the triad can be seen in isolation. In terms of cognitive theories and brain imaging, there is also no single explanation for the three aspects of the triad. Dr. Happé noted, however, that when impairments in all three domains occur together, there may be a qualitative shift, perhaps reflecting a stripping away of the individual's ability to compensate. She concluded by noting the need to consider the separability of the domains of the triad when considering a dimensional approach to the diagnosis of autism spectrum disorders.

The second panel addressed the question how are fixated interests and stereotypes related to each other, to autism, and to obsessions and compulsions? In his introduction to the panel, Edwin H. Cook, Jr., M.D., (Chicago, IL) noted that restricted and repetitive behaviors are currently de-emphasized relative to social impairment. Why should a child with mild social and communicative impairment whose main impairment is disabling restrictive and repetitive behaviors be considered to have less likelihood of autistic disorder? Is our lack of emphasis on severity of this area justified by the data or is it based on our "preoccupation" with social and communication function? Why do we have use of stereotyped language in the communication domain rather than the restricted and repetitive behavior domain? Dr. Cook raised the question of whether repetitive and restricted behaviors would be better split into two facets (i.e., insistence on sameness and repetitive sensory motor behavior), noting that they might have different behavioral and treatment implications (e.g., elements of insistence on sameness are responsive to SSRIs in some patients; it may make more sense to treat insistence on sameness as a single entity since it does get in the way of other interventions, in comparison to repetitive sensory motor behavior [RSMB] which often is reduced with optimal educational interventions, even though the interventions are not directed specifically at RSMB). James Bodfish, Ph.D., (Chapel Hill, NC), in his presentation, noted that according to factor analyses, there is likely more than one variety of repetitive behavior, with some analyses suggesting that insistence on sameness and compulsions represent a higher order factor and repetitive sensory motor behavior a lower order factor. He also questioned which variety is relatively more specific to autism (repetitive motor behaviors including repetitive use of objects, or sameness, rituals, compulsions, or fixated interests; different studies have conflicting results); which variety has the earliest onset and persists with age (all varieties maintain with age although severity tends to diminish). Finally, regarding the role of repetitive behaviors in the diagnostic criteria for autism, multiple studies have shown that severity of sameness/rituals (but not repetitive motor behavior) is independent of social language deficits, that repetitive behaviors vary continuously within autism (i.e., they do not form taxa or subtypes); that increased repetitive behaviors are associated with increased social and/or language deficits (i.e., severity of the two domains runs together); and that early repetitive behaviors predict later social / language deficits. Susan Swedo, M.D., (Bethesda, MD), in her presentation, noted how little data has been reported regarding the difference between fixated interests in autism and obsessive-compulsive symptoms in obsessive-compulsive disorder (OCD), noting that there may be a clear difference between childhood onset obsessions and adult-onset obsessions. Differences in treatment response, patterns of comorbidity and neuroimaging findings suggest that in adults, obsessions seem to fit best with anxiety disorders and in children are more closely linked to attention deficit hyperactivity disorder and tic disorders. Regarding the difference between stereotypies in ASD and compulsions in OCD, the two symptoms are more similar than different in presentation. For example, when the repetitive behavior is interrupted, children respond negatively, regardless of whether the behavior is a compulsion or a stereotypy. Dr. Swedo noted three possible hypotheses regarding the relationship: that symptoms in autism and OCD are the same phenomena and result from similar etiologies; that they are the same behavioral abnormality, but represent different etiologies; or that symptoms in autism and OCD only appear to be similar but differ in nature and etiopathogenesis. Comparing ASD and obsessive-compulsive personality disorder (OCPD), similarities between them include rigidity, need for sameness, and individuals being "cold" and socially isolated; differences include age at onset (earlier in ASD), degree of impairment (greater in ASD), and presence of comorbid symptoms (more in ASD).

The third panel addressed the question how does the presentation of autism change across the lifespan? In her introduction, Catherine Lord, Ph.D., (Ann Arbor, MI) commented that one of the real improvements in *DSM-IV* was to include criterion items that would apply to both pre-school and school-age children; however, the items still do not adequately apply to toddlers, adolescents, and adults. When assessing toddlers, one challenge is to get reliable information from a parent who may not be familiar with normal childhood development; for adolescents and adults, compensatory strategies and learning might alter the presentation. Interpreting longitudinal data can be challenging because the proportion of children who have difficulties with the ASD domains change over time, as do factor loadings. For example, repetitive behaviors start early in the course and persist over time, but the number of behaviors goes down and they tend not to be as interfering. On the other hand, insistence on sameness tends to start later and increases slightly. Amy Wetherby, Ph.D., (Tallahassee, FL) noted that prospective studies of general population samples have documented core deficits in social communication, fixated interests (e.g., sticky attention to objects) and repetitive behaviors in children with ASD in the second year. Deceleration of development may be characteristic of the unfolding of diagnostic features of ASD over the second year, making screening and early detection more challenging. Social communication and repetitive behaviors are independent constructs early in the second year and become



intertwined by late in the second year, with repetitive behaviors contributing to social affect deficits at 3 years of age. These early core deficits appear to have a cascading effect that impacts the children's learning environment by limiting what they can get out of it. Keith Widaman, Ph.D., (Davis, CA), in his presentation, looked at lifespan changes from the perspective of mental retardation. Cross-sectional studies of intelligence have shown that there are substantial improvements in many areas until the developmental period ends around age 20; after that point, stability is more likely. For mental retardation, which is considered a developmental disorder, the diagnosis is supposed to be made in the first 18 years of life. Does it therefore make sense to make a diagnosis of ASD and intellectual disabilities in someone presenting at age 50? An empirical basis for making long term predictions about outcome is lacking for individuals with autism. Harry H. Wright, M.D., (Columbia, SC), noted that despite a consensus that autism nearly always develops before 3 years of age, it is only recently that significant information on the early presentation of ASD in very young (birth to 3 years of age) children has been reported. He called for similar efforts to develop developmentally sensitive criteria and diagnostic algorithms across the lifespan, especially in early and middle adulthood. Dr. Wright recounted how his clinic has been getting referrals for evaluation of adolescent and adult family members (e.g., older siblings, uncles) of young children diagnosed with autism but there are no guidelines for making a diagnosis of ASD in such older individuals; adult examples are needed for the various autism criteria. This may be a particular issue for African-American families who are typically referred at a later age than their Caucasian counterparts.

The fourth panel addressed the question how does developmental regression (and particularly Childhood Disintegrative Disorder) fit into the autism spectrum? In her introduction, Sarah J. Spence, M.D., Ph.D., (Bethesda, MD) raised a number of questions about the construct of regression in ASD, including what is it and how commonly does it occur? Does regression represent true loss of skills versus just a plateau, and which skills should define a regression? Does it require normal development to precede it? When does it happen? What causes it? How important are medical factors? Is it specific to ASDs? Regression is currently only included in the diagnostic criteria in Childhood Disintegrative Disorder (CDD), where it is required. Clinically it is commonly seen in Rett Syndrome but not included in the criteria, and is not even mentioned in Autistic Disorder, Asperger's Disorder, or PDD-NOS, although it is known to occur fairly frequently. Childhood Disintegrative Disorder was first mentioned by Heller in 1908 and was first included in the *DSM* starting with *DSM-IV*. The available literature on CDD consists of case reports and a few case series. The paucity of reports is confirmation that CDD is a rare condition, with prevalence thought to be 1.1 to 6.4 per 100,000. It was once assumed that various presentations of CDD have a common medical etiopathogenesis, but a cause is not identified in most cases. Dr. Spence summarized some of the challenges in defining the role of regression in CDD and other ASDs as follows: 1) determining the validity of the age requirement (24 months-10 years); 2) operationalizing the definition of regression; 3) close examination of pathogenesis and clarification of the role of co-morbid medical diagnoses; and 4) determining its impact on prognosis and response to intervention. In his presentation, Hiroshi Kurita, M.D., (Tokyo, Japan) argued that although CDD is quite rare and research on CDD very scarce, there is no convincing evidence to abolish or merge it with autistic disorder, and that it should be preserved as an independent disorder. He made a number of specific suggestions to improve the CDD criteria set, including: 1) changing the requirement in criterion A for the regression history from "apparently normal development" to "no clinically significant delay or abnormality in development"; 2) deleting motor skills regression from the areas of regression in criterion B because of scarcity; and 3) in criterion D, having the diagnosis of CDD pre-empt a diagnosis of autistic disorder so that CDD with onset before age 3 is not diagnosed as autistic disorder (one-third to one-half of CDD patients show their regression between ages 2 and 3). Compared with autistic disorder, CDD has no significant difference in clinical symptomatology apart from its higher incidences of epilepsy and EEG abnormalities. Dr. Kurita concluded by noting that given the rarity of CDD, a standard format of evaluating a possible CDD case or a case with a history of regression is needed to facilitate early detection and research of CDD and other PDD with regression. Pauline A. Filipek, M.D., (Irvine, CA) showed prospective video clips of an infant aged 13 months through 26 months that illustrated apparently normal development at age 13 months, with gestures and 6 to 7 spontaneous words. One month later, he presented to the clinic with a loss of response to name, followed by loss of his 6 to 7 words, onset of highly repetitive play and loss of eye contact, which progressed to frank autistic disorder by age 24 months. This sequence raised questions about what separates autistic regression from CDD -- how often does regression occur in autistic disorder? Is CDD simply autistic regression that occurs later, after age 24 months? During the ensuing discussion, it was pointed out that regression may be a more common feature of autism than was previously thought with some prospective studies indicating that a loss of skills is the rule rather than the exception. In regressive autism, the skills are lost in the second year of life, while in "early onset" autism, skills are lost in the first year of life. There was general agreement that symptom onset is on a continuum between regression and non-regression and that defining the borders between the two can be difficult. Diagnostic certainty is particularly problematic because most parents are not going to pick up a regression of acquired skills unless the child has acquired language which then is lost.

The fifth panel addressed the question Asperger's Disorder -- is it Autism? In her introduction, Francesca G. Happé, Ph.D., (London, UK) raised some of the key questions that have arisen regarding the diagnosis of Asperger's Disorder, which was introduced into *DSM-IV* in 1994. These questions include: is there an 'Asperger' subgroup of autism with distinct cause, course, cognitive profile, and intervention needs, and if so, what is its relation to other ASDs? Asperger's disorder is essentially defined as meeting criteria for autism without the language impairment. Lorna Wing introduced the term in 1981 to aid recognition of the part of the autism spectrum with good IQ and language. It has increased awareness and recognition and helped to clarify the core deficits of ASD, but also increases the possibility that there may be over-diagnosis of ASD. Asperger's disorder has also had an impact on family studies of autism with regard to what we recognize as "caseness." Dr. Happe noted that the current criteria do not work: they do not allow for developmental change, the early language criteria do not demarcate groups with different prognoses, it is hard to apply the diagnosis for adult cases, and there is no clear conceptual basis for the diagnosis. Dr. Happe concluded that although there is a recognizable Asperger's type and that some cases of classic autism grow into this picture, she wonders whether there may be a better classification schema. Sally Ozonoff, Ph.D., (Sacramento, CA), in her presentation, compared high functioning autism (HFA) with Asperger's, and noted that there were few differences in their definitional *DSM-IV* criteria; both require two social symptoms and one repetitive/stereotyped symptom, both are in the average range intellectually and have current fluent language. The main criterion distinguishing the two disorders is the

requirement in Asperger's that onset of language occurs at the expected time, e.g., single words by age 2. Dr. Ozonoff noted that it is difficult to evaluate the literature since definitions vary across studies and that many children who are thought clinically to have Asperger's actually meet criteria for autism (which supercedes a diagnosis of Asperger's). There is some evidence to suggest that Asperger's and HFA do not represent distinct disorders: they co-occur in the same families and do not "breed true" (i.e., family members of patients with Asperger's have HFA and family members of patients with HFA have Asperger's); children with autism who develop language have similar outcome to Asperger's; HFA and Asperger's are indistinguishable by school-age; and although studies find better language skills and/or verbal IQ in Asperger's, multiple studies have found no group differences in other neuropsychological domains.

The sixth panel addressed the question, Is Autism a Life-Long Diagnosis? Bryan H. King, M.D., Ph.D., (Seattle, WA) introduced the panel by asking if one outgrows a diagnosis or it remits, (particularly in the context of genetic underpinnings), is it still there? Residual language deficits have been demonstrated in some children with a well-documented history of autism who have gone on to have excellent outcomes. As children age, they tend to lose some of the severity of their illness so that the diagnosis can change from autistic disorder to PDD-NOS. A problem is caused by linking a diagnosis to the severity of manifestations of the symptoms. This causes difficulties for service provision and for clinical trials; for example, the FDA will not allow for an indication that was created for autism to transfer over to PDD-NOS, even though it may be the same children who have the two different diagnoses (ASD when young and PDD-NOS as they develop further). The current classification mixes categorical definition with the severity of disorder. Eric Fombonne, M.D., (Montreal, Canada) began his presentation by noting that a diagnosis of autistic disorder is usually highly stable; less than 7% fall out of the autistic spectrum on follow-up. On the other hand, children with ASD who do move out of the spectrum are most likely to start out as PDD-NOS, reflected the very mixed bag of patients that fall under this rubric. It is possible that PDD-NOS represents a lower "dose" of autism (i.e., still ASD); it could be a phenocopy (i.e., non-ASD that present with PDD symptoms, including genetic syndromes such as Rett disorder); it could be the result of environmental exposure, (such as fetal alcohol syndrome), or it could result from plain measurement error. When PDD-NOS is no longer present, is the phenotype qualitatively the same but the associated impairment has become minimal (i.e., is it only the impairment that has disappeared) or is there evidence for true remission of autism? Long term follow-up and adult studies are essential to address the question of remission. With respect to considerations for *DSM-V*, Dr. Fombonne concluded by noting that the heterogeneity of the PDD-NOS diagnosis is problematic as there are at least two ways to meet criteria: the pattern of symptoms is the same as in ASD (all domains affected) but of lesser severity, or the pattern may be different (one or two domains only). It may be useful in the future to measure/document the impairment associated with each domain (rather than globally). Finally, age of onset is a further problem as it often depends on parental recognition or retrospective recall. Craig Newschaffer, Ph.D., (Philadelphia, PA), in his presentation, noted that we are still at a point where the connections between pathology and the phenotype of autism are not understood. How the manifestations of underlying pathology change over time and what, if any correlations exist between pathology and clinical phenotype are still unknown. Regarding the evolution of the behavioral phenotype over the life course, there are very few cross-sectional studies in adolescents and adults, and even fewer longitudinal studies. The lack of availability of age-appropriate measures may contribute to this lack. The few small sample studies that have been published focus on the loss of diagnosis (typically in children) and presentation of previously undiagnosed adults. From the clinical perspective, should the diagnosis of autism be lost when symptom-based criteria are no longer met? This has potential impact on treatment plans and access to services for the child or young adult and their family. The diagnosis of ASD in symptomatic adults is also difficult, due to the lack of tools appropriate for use in adults and the difficulty in obtaining the developmental data required to make a diagnosis of ASD (which must present before age 3 years). The differential diagnosis is particularly challenging in adults because of the number of other disorders that affect the social domain. These limitations suggest that other features (e.g., nonverbal communication, prosody, subtle use of language, posture, etc.) might prove to be better diagnostic criteria for adults? Without such clarity, it is questionable whether the prevalence of ASD in adult populations can be validity and accurately estimated through epidemiological studies.

The seventh panel addressed the question of how does comorbidity affects symptoms of Autism? In her introduction to the panel, Sally Rogers, Ph.D., (Sacramento, CA) noted that other developmental disorders occur commonly with autism (e.g., up to 86% also have non-verbal learning disorders) as well as other psychiatric disorders (e.g., 20-30% with affective disorders, 33-75% with ADHD), and various medical conditions (10-37%, with the rate depending on the severity of the degree of intellectual disability). Dr. Rogers argued that one way to address this comorbidity is to adopt a dimensional approach which could address sociability and social capacities, communication, intellect, activity level, motor skills and movement, mood and temperament, academic abilities, adaptive behavior, maladaptive behavior/psychiatric symptoms, and health. Autism could be viewed in the same way as we do intellectual disabilities (i.e., IQ) -- as a final common behavioral pathway of many different biological etiologies: "the autisms," as opposed to our current view of autism as primarily a familial genetically-determined disorder with comorbidities occurring more frequently in the more severe cases. Tony Charman, Ph.D., (London, UK) presented on the topic of autism and intellectual disability and noted that two recent population-based surveys assessing ASD at different levels of intellectual disability found rates of 9-12% for individuals with mild ID (IQ 50-70) and rates of 26-30% for moderate ID (IQ 35-50). Rates of ASD in those with more severe ID (IQ<35) are not known. Although in the current ASD criteria only peer relationships and conversational abilities are explicitly related to developmental and language levels, other symptoms are dependent on developmental maturation as well. Should there be different symptom thresholds depending on IQ? For example, looking at repetitive behaviors in ASD, there are difference prevalence rates in high versus low IQ patients. Comorbidity patterns are thought to differ by intellectual abilities, but this may be the result of diagnostic overshadowing, which often leads to underdiagnosis of psychiatric comorbidity, i.e., if there is already a diagnosis of ASD, why give an additional psychiatric diagnosis? Thomas Anders, M.D., (Sacramento, CA) presented on sleep in children with neurodevelopmental disorders, noting that anecdotally, sleep disorders are a major problem in ASD. In a study using an actigraph to measure sleep in children with autism or developmental disabilities, and among typically developing children, children with autism had the least amount of sleep (less 24-hour sleep time and less nap time); those with developmental disabilities were intermediate between the children with autism and the typically developing controls; however, children with developmental disabilities had the most fragmented sleep. Dr. Anders concluded that children with autism likely have a

clock problem compared with children with other developmental disabilities. Walter Kaufmann, M.D., (Baltimore, MD) presented on ASD and cognition. He proposed three alternative hypotheses for the relationship between ASD and intellectual disability (ID): 1) ASD is non-specific and is simply another manifestation of severe neurobiological impairment; 2) it is selective but also a reflection of decreased communication skills; and 3) ASD in ID is a selective and specific impairment in social interaction. In Down syndrome, children who meet criteria for ASD tend to have IQs in the severe and profound range whereas in Fragile X, ASD diagnoses are concentrated in the moderate IQ range. However, low IQ *per se* has a minimal influence upon ASD status in ID. Dr. Kaufmann concluded that although low IQ is a predisposing factor to ASD, not every child with severe to profound ID meets criteria for ASD. Qualitative impairments of social interaction (in joint attention, in shared enjoyment, perhaps others), appear to be relatively independent of mental age and are found in individuals with severe-profound ID. Among individuals with both ID and ASD, the presence of repetitive and stereotypic behavior is more severe and complex than would be expected on the basis of the lower mental age alone. However, IQ less than 25 to 30 is a limiting factor for behavioral interpretation given that such individuals do not have the behavioral repertoire characteristic of ASD.

The eighth panel addressed the question what role should neurobiology play in the DSM-V diagnostic criteria for autism? In his introduction to the panel, Joe Piven, M.D., (Chapel Hill, NC) noted that even though autism is defined exclusively in *DSM-IV* in terms of behavioral criteria, evidence for the biological basis of autism is growing with studies demonstrating variable support and variable explanatory power for biological variables. An increasing number of investigations are demonstrating associations between ASD and genetic aberrations (e.g., chromosome 15 duplications, chromosome 16 deletions, familial types), as well as biological markers (e.g., neurotransmitter levels), neuroimaging results (e.g., brain volume), head circumference (e.g., macrocephaly), electrophysiological testing (e.g., ERP, EEG) and neuropsychological assessments (e.g., face processing). However, these findings are not sufficiently specific or cohesive enough to allow for the identification of clinically meaningful subgroups or to be used as risk markers. Regarding how to incorporate subgroups of ASDs with an identifiable etiology (e.g., Fragile X, tuberous sclerosis) into the diagnostic framework, options include listing the medical condition on Axis III, including a subtyping scheme on Axis I (e.g., autism, Fragile X type), or excluding it from the diagnosis altogether, as is now done with Rett's syndrome. Finally, given the rapid pace of research on the biological basis of the 'autisms', it will be important to construct a flexible diagnostic system that is able to incorporate new information before the appearance of DSM-VI. Catherine Barthelemy, M.D., Ph.D.m (Tours, France) then presented data demonstrating how electrophysiology combined with genetics can help to define new markers for better phenotypes and perhaps endophenotypes of autism. She described a series of studies focusing on event related potentials in the detection of abnormalities in the processing of social information, especially faces and voice, hypothesizing that the need for sameness in autism could be rooted in abnormal sensitivity to change. In these studies, latency of response to automatic change is significantly shorter in children with autism compared to normal children and may be a good index of the reaction to change. Moreover, the shorter the latency, the more severe the reaction to change measured by behavioral scales. Dr. Barthelemy concluded by noting that the advantages of electrophysiological markers include that they are objective measurements which are quantifiable (in terms of amplitude, latency, etc), non-invasive, low cost, and easy to apply to both children and adults. Further studies are needed on large populations to determine sensitivity, specificity (especially with regard to other disorders such as OCD) and stability over time. Edwin H. Cook, Jr., M.D., (Chicago, IL) then presented on the genetics of autism. The most common model for autism, called the common variant-common disease model, postulates that there are various risk variants that contribute to autism. For example, if there are five risk variants, one needs to have hits on all five variants for the disorder; hits on four variants would lead to ASDNOS. It is thought that the vast majority of autism cases are multifactorial. Another model is the "big hit" model, in which autism is caused by a genetic abnormality with higher penetrance; examples include chromosome 15q11-13 duplication or triplication (0.5-3%), Fragile X (0.5-3%), 16p11.2 deletion (0.5-1%), SHANK3 mutation (0.5-1%), etc. The most likely model is that these "less complex" cases represent situations where the chromosomal or single gene variant is equivalent to a number of smaller effect variants. It is important to understand, however, that the so-called etiological syndromes have substantial variability in terms of behavioral manifestations: a diagnosis of Fragile X, maternal 15q11-q13 duplication, VCFS, SHANK3 mutation, or 16p11.2 deletion is NOT equivalent to diagnosis of an ASD and even when there is a strong association, knowing the genetic defect does not provide a predictive description of that child's behavioral manifestations. Some syndromes are associated with patterns of symptoms: for example, Fragile X and gaze aversion, maternal 15q11-q13 duplication and mood lability. Other syndromes (e.g., 16p11.2 deletions) are without obvious distinguishing features including variable cognitive function. Finally, many patients have unique submicroscopic deletions and duplications and many genetic abnormalities associated with ASD may be *de novo* and non-recurrent. Walter Kaufmann, M.D., (Baltimore, MD) presented on Rett Syndrome and ASD, noting that up to 75% of researchers feel that Rett should not be in a separate category in the ASD section. In Rett, autistic features are sometimes indistinguishable from autism but they are only present during a certain phase of the illness (i.e., between 1 and 3 years of age) and will get better without treatment. Those girls who do not have the marked motor features most characteristic of Rett (i.e., increased tone, dyspraxic gate, hand-wringing) are more likely to be diagnosed as idiopathic autism because genetic testing does not seem warranted. Finally, he presented on two biomarkers that suggest the potential future use of imaging and molecular profiles in the diagnosis of autism spectrum disorders: abnormal size of the posterior-superior vermis (absolute hypoplasia in idiopathic ASD, relative hyperplasia in Fragile X + ASD) and lymphoid cell abnormalities in cytoplasmic *FMR1* interacting protein 1 (*CYFIP1*) pathway expression in both Fragile X and chromosome 15 duplication associated with ASD.

The final panel addressed International, Cultural, and Gender considerations in the diagnosis of Autistic Spectrum Disorders. In his introduction, Poul Thorsen, M.D., Ph.D., (Aarhus, Denmark) focused on gender differences, noting that the male-female ratio for a diagnosis of ASD is 5:1 whereas the ratio for childhood autism is 3-4:1. The rate of recurrence in siblings of affected individuals is 2-8%, which is much greater than the risk in the general population. A history of low birth weight and/or being small-for-gestational age was more common among high-functioning girls with autism than among their unaffected female siblings whereas there were no differences in frequency of low weight between high functioning males with autism and their male siblings. Autism sex ratio (male: female) is lower in individuals with ID than in individuals with normal cognitive functioning and lower in individuals with significant dysmorphology or microcephaly

than those without. Data from a Danish psychiatry registry of children born from 1990 to 1999 found that males on average met 0.63 more items than females. Males on average met 0.29 more items concerning impaired communication and 0.28 more items concerning restricted behaviors than females. For autism cases without mental retardation, males overall met on average 0.69 more items than females and on average 0.28 more items concerning restricted behaviors when adjusting for age. He concluded that since males consistently met more autism items than females, the current diagnostic criteria may favor the diagnosis of autism in males. In her presentation, Diana E. Schendel, Ph.D., (Atlanta, GA) began by discussing the difficulties in trying to connect prevalence studies and diagnostic criteria given that the connection between the diagnostic criteria and case features is not a direct line; when you start with the diagnostic criteria, even if they are being implemented directly, the implementation process will influence the outcome or features of the case group you find. For example, most studies need to rely on an agency to identify cases and often agencies differ in the characteristics of their case group, possibly due to differences in populations being served. As another example, a Danish study which compared rates of autism to other childhood psychiatric disorders has shown a similar increase in incidence for these other disorders over time, suggesting that the similar trends reflect the shared processes by which cases with these different disorders have been identified. As a third example, another administrative process that may influence case group features is the significant shift in age of diagnosis over time. In a Danish study, shifts in age of diagnosis, especially substantial acceleration at younger ages, artificially inflated the differences in observed risk for autism among young children in more recent cohorts compared to older cohorts. Autism trends based on data with incomplete follow up (i.e., they lack follow-up to the age at which all individuals have been identified) can be confounded by changes in age of diagnosis over time. To the extent that these and other administrative factors influence observed prevalence and/or distribution of behavioral phenotypes in a case group (e.g. autism in toddlers vs. older ages) observed at a specific point in time, then the case group profile of "What is autism?" may vary accordingly. In his presentation, Kang-E Michael Hong, M.D., (Seoul, South Korea) raised the question of whether it is possible that some cases of ASD are caused by environmental factors by examining three sets of data. The first set of data came from studies of Reactive Attachment Disorder (RAD) in Korea. There are big socio-cultural changes in Korea with rapid modernization that has brought changes in child-rearing. One result appears to be increased reports of RAD among children who have not suffered gross physical abuse or neglect; instead these are children who are thought to have been subjected to pure emotional and social deprivation. These so-called RAD children appear clinically very similar to autistic children and have been labeled as having a "Korean syndrome of attachment" mimicking ASD. This raises the question of whether RAD is totally separate from PDD, i.e., is it possible that some cases constitute a type of ASD? Other sets of data come from the recent studies of institutionalized children in Romania in which there is a close association between duration of deprivation and severity of attachment disorder, with many of the children described as "quasi-autistic" (at least in early childhood). A third set of data potentially supporting the premise that ASD may be related to care-giving comes from the huge increase in prevalence rates of autistic disorders. Although the main reasons for rising prevalence are likely to be improvement in ascertainment and broadened definition of ASD, it is possible that changes in child rearing practices and problems of parental emotional unavailability during early infancy may play an etiological role in modernizing societies. Dr. Hong concluded by proposing a research agenda on the role of environmental risk factors in the development of ASD, including: 1) definitive research on environmental/experiential factors, particularly quality of caretaking, as a modifier or etiological contributor in ASD; 2) continuing the need to separate classical autism and the rest of ASD in carrying out further longitudinal studies with regard to etiology, phenotype, progress patterns and intervention; 3) a need for RAD and ASD research camps to converge to decide the relationship between these diagnostic categories; and 4) application of the concept of sensitive period of social development and attachment in understanding, studying and intervening ASD. In his presentation, Craig Newschaffer, Ph.D., (Philadelphia, PA) considered the range of factors that must be taken into account when trying to explain differences in U.S. diagnostic criteria and prevalence rates compared to those found in Europe and Asia. These factors include differences in study methodology, diagnostic criteria, community diagnostic tendencies, cultural context, calendar time, and true variations in the underlying risk. Language and cultural factors are especially important considerations, making adaptation of tools to other languages and cultures particularly challenging. For example, in a Chinese pilot study, when translating diagnostic interviews into Mandarin, it was discovered that there is no distinction between singleton and plural or between past and present tense, creating great difficulties with historical assessments. Furthermore, the cultural norm in China is for gestures to be discouraged and for persistence to be highly valued. Dr. Newschaffer concluded that there will be an explosion of epidemiologic studies worldwide and that work is beginning on how these studies can be conducted in more culturally robust ways.

Upon conclusion of the panels, participants convened into three breakout groups to formulate recommendations for research and suggestions for possible changes to be considered for *DSM-V* and *ICD-11*.

The first breakout group recommended the following revisions in the diagnostic criteria: 1) examine the age of onset requirements for Childhood Disintegrative Disorder and Autistic Disorder; 2) add more descriptive text to describe how to apply the criteria to different developmental levels and ages (i.e., adult and young child examples); 3) revise criteria for imaginative play (it is too restrictive in terms of the age that it is appropriate for); 4) revise the criterion for peer relationships given that it is too broad (most psychiatric disorders affect peer relationships); and 5) revise communication criteria (item 2a, delay in or total lack of spoken language). The group also suggested the following be considered: 1) explore the possibility of taking IQ into account in the diagnostic criteria either by making distinctions between children above/below IQ 50 and/or by adding text and examples; 2) clarifying the role and importance of current versus historical symptoms (e.g., if the individual had a symptom earlier such as echolalia but not currently, does it still count?); 3) operationalizing the criteria for PDD-NOS in order to standardize the meaning of the diagnosis (currently, PDD-NOS is a "wastebasket" category which includes individuals with widely disparate symptom patterns): options include counting items contributing to diagnosis and/or identifying particular subgroups; 4) adding a requirement for impairment (which also would need to be operationalized); 5) adding a broader autism phenotype with qualitative, personality language, or behavioral features.

The second breakout group made the following recommendations. With respect to evidence supportive of the *DSM-IV* approach, *DSM-V* should continue to include aspects of the three domains (i.e., impairment in social interaction, impairment in communication; and restricted or repetitive interests or activities) although the group did not agree it

should necessarily be a triad. *DSM-V* should also continue to require early onset before age 3; and to keep the behavioral syndromal approach. Changes in *DSM-V* recommended by the group include: 1) eliminating the exclusion for Rett's disorder and Childhood Disintegrative Disorders and instead adding a specifier to indicate that it is "associated with diagnosed general medical condition; 2) eliminating Rett's Disorder from ASD; 3) eliminating CDD as distinct category and instead modifying the age at onset in Autistic Disorder to be: "onset by age 3 (or by age 6 years in cases where there is a normal period of development followed by clinically significant regression in acquired skills)" and adding a specifier to indicate "with late onset and regression" so that such cases can be identified; 4) regression needs to be better characterized (e.g., description of patterns in the text); 5) given that children with profound ID could meet criteria for Autistic Disorder as a result of nonspecific cognitive disabilities; add a clause to criteria advising that developmental level should be taken into account when making the diagnosis; 6) make diagnostic criteria more developmentally appropriate by adding examples of how each criterion is manifest across the life span, especially for infants, toddlers, and adults; 7) eliminate Asperger's Disorder from this section; 8) change the name of the diagnostic grouping from PDD to ASD; 9) put symptoms inside a dimensionality framework that integrates with other disorders; 10) consider adding cognitive style as an autism symptom; 11) add optional specifiers to the NOS category (which would be named ASDNOS in *DSM-V*) (e.g., subthreshold symptom count, atypical age at onset, subthreshold triad distribution); 12) separate symptom assessment from disability by adding a criterion that establishes caseness based on exceeding a cut-point on functioning scale (to be determined); 13) emphasize use of "partial" and "full remission" to indicate symptom improvement; and 14) eliminate exclusion of ADHD from ASD (i.e., allow comorbid diagnosis of ADHD and ASD). Finally, the group recommended that data sets be combined for meta-analysis in order to: 1) examine longitudinal changes over time; 2) determine developmentally appropriate examples; 3) look at presentations in adolescents and adults; 4) examine effects of changing criteria on prevalence; 5) determine effects of combining social impairment and communication domains; 6) examine the applicability of symptoms with respect to gender; 7) gather sensitivity and specificity data for individual items for possible weighting of items or re-ordering; 8) examine patterns of comorbidity in population-based samples; 9) evaluate symptom presentation to identify clinically meaningful subtypes of ASD; and 10) design methodologies to explore the relationship between excluded disorders (e.g., ADHD) and ASD in order to determine whether treatment response is different in comorbid cases and whether excluded symptoms are best understood as associated features of ASD (in which case the hierarchy should be retained) versus an independent disorder (in which case the hierarchy should be eliminated). Finally, the group recommended adding dimensions that should be rated after making diagnosis of AD or ASDNOS to further identify functioning and impairment.

The third breakout group made the following recommendations: 1) delete Asperger's disorder; 2) delete CDD; and 3) create an ASD with two types: Type I would be for prototypical cases characterized by problems in social interaction, social communication, and repetitive behaviors or preoccupations, and Type II is for atypical cases. Data needed to inform such a decision include: 1) the number of criteria to be met for Type I and Type II (at least one in each category); 2) core symptomatology over various ages and developmental stages; 3) clarification of the requirements for diagnosis in females and diverse cultural groups; 4) a definition of impairment at different ages and developmental stages; and 5) consideration of effects of IQ and of comorbid diagnoses. Other specific suggestions include: 1) determining whether obsessive-compulsive symptoms occurring in ASD are part of the ASD or warrant a separate diagnosis of OCD; 2) removing the ADHD exclusion; 3) adding better examples for criterion items across the lifespan; 4) adopting a better definition for regression; 5) determining whether ASD remits and what a residual state might look like; and 6) consider genetics as a modifier versus continuing to code it on Axis III.

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EXHIBIT 11



**Statement regarding Dr. Poul Thorsen's involvement in Aarhus University projects**

Aarhus University has decided to issue this statement in response to a number of requests on the part of CDC Denmark project partners.

Dato: 22. januar 2010  
Sagsnr.: AU-2010-179-012  
Ref: pmm

Side 1/2

Issue: The extent and nature of Dr. Poul Thorsen's continued involvement in the CDC Denmark project for which he once provided primary scientific and administrative oversight, as well as of his continued relation to Aarhus University.

Background: The Danish Agency for Science, Technology and Innovation (DASTI) has been a grant recipient as part of a cooperative agreement with the US National Center for Birth Defects and Developmental Disabilities, CDC, since 2001. The grant has been administered by Odense University Hospital and Aarhus University (AU) under the direction of Dr. Poul Thorsen. The grant has multiple components and involves collaborators at other institutions in Denmark, including the University of Copenhagen and SSI (Statens Serum Institut). This successful collaboration has resulted in numerous valuable scientific results, and many more are forthcoming.

Unfortunately, a considerable shortfall in funding at Aarhus University associated with the CDC grant was discovered. In investigating the shortfalls associated with the grant, DASTI and Aarhus University became aware of two alleged CDC funding documents as well as a letter regarding funding commitments allegedly written by Randolph B. Williams of CDC's Procurement Grants Office which was used to secure advances from Aarhus University. Upon investigation by CDC, a suspicion arose that the documents are forgeries.

DASTI conducted an internal investigation of the authenticity of the documents and have filed a police report with no specific person named in the filing. A police investigation is ongoing.



In March 2009, Dr. Thorsen resigned his faculty position at Aarhus University. In the meantime, it has come to the attention of Aarhus University that Dr Thomsen has continued to act in such a manner as to create the impression that he still retains a connection to Aarhus University after the termination of his employment by the university. Furthermore, it has come to the attention of Aarhus University that Dr Poul Thorsen has held full-time positions at both Emory University and Aarhus University simultaneously. Dr Thorsens double Full-time employment was unauthorised by Aarhus University, and he engaged in this employment situation despite the express prohibition of Aarhus University.

Conclusion: Aarhus University wishes to confirm that Dr Poul Thorsen no longer has any connection to Aarhus University, and that Aarhus University will not be able to collaborate with Poul Thorsen in the future. To the extent that other parties collaborating with Aarhus University wish to draw on Poul Thorsen's expertise, Aarhus University will only accept such collaboration if it has the purpose of securing data or protecting the interests of participating researchers and funding agencies.

Jørgen Jørgensen

Managing Director



EXHIBIT 12

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# DANISH HIGH-PROFILE TAX CASE POSTPONED AGAIN

March 14, 2012

DANISH HIGH-PROFILE TAX CASE POSTPONED AGAIN

By Ulla Danielsen, journalist, DK-Copenhagen

A Danish case of gross tax evasion is being postponed one time after another.

The defendant in the case is former autism researcher at Aarhus University (AU) Poul Thorsen.

Thorsen's name will ring familiar to many, as his autism research was sponsored substantially by the American health agency Centers for Disease Control and Prevention (CDC).

Danish daily INFORMATION in 2010 reported, that Poul Thorsen's research center Nanea at Aarhus University in 2000 received a grant of 7,8 million dollar from the American health institution Centers for Disease Control and Prevention (CDC).

The grant was administered by Danish Agency for Science, Technology and Innovation (DASTI) under the direction of Poul Thorsen.

In 2007 the project was prolonged by a new grant from CDC of 8,2 million dollar.

This is the financial context that makes the case of gross tax evasion a matter of public interest.

Moreover in 2011 the tax-case was postponed three times. This year there has also been delays.

Of late it was scheduled for March 9 and afterwards for March 15. However, this does not mean that the proceedings will begin on March 15.

In February the city court in Aarhus rejected a claim by the defence to have the case dismissed.

The defence claimed that the indictment was imprecise.

Next step for the defence was to appeal the city court's decision to Danish High Court.

And now, in spite of the case being on schedule the High Court has not yet made up its mind.

According to police assessor Lars Petersen from the police of Eastern Jutland, as late as Tuesday 13, no order had been issued.

The city court in Aarhus has adapted to this somewhat awkward situation by postponing the case that now, maybe, will begin on March 29.

Poul Thorsen's counsel for the defence is lawyer Jan Schneider from the Danish lawfirm of Tommy V. Christiansen. This firm specializes in tax matters.

In 2009, the prosecution charged Poul Thorsen with gross tax evasion in the amount of more than 6,4 million DKK.

For this deed, the Prosecution claims, that Poul Thorsen must be punished with prison. Poul Thorsen on the other hand – according to a Danish news agency – claims that he is not guilty.

The indictment states that, during the years 2001-2005, Poul Thorsen evaded income tax on 6,430,768 DKK from fees, salary or the like.

By these illegal acts, the Danish tax authority was deprived of 3,470,020 DKK that it was owed.

Further, the defendant has been accused of intentionally evading 514,455 DKK in contributions to the labour market taxes owed to the Danish tax authority during the period from 2001 through 2005.

Four days have been allocated for the proceedings. However, everything depends on the ruling of Danish High Court.

Hopefully the High Court will at least perpherially consider the recent revisions recommended by The Financial Action Task Force (FATF), an international body that addresses financial issues. An increased focus on tax crimes was one of the FATF's recent key recommendations.

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# **BREAKING NEWS: DANISH HIGH COURT DISMISSES CASE OF GROSS TAX EVASION AGAINST FORMER DANISH AUTISM RESEARCHER POUL THORSEN**

March 26, 2012

**BREAKING NEWS: DANISH HIGH COURT DISMISSES CASE OF GROSS TAX EVASION AGAINST FORMER DANISH AUTISM RESEARCHER POUL THORSEN**

By Ulla Danielsen, journalist, DK-Copenhagen

Danish High Court (Vestre Landsret) on March 23, 2012 decided, that the case against former Danish autism researcher Poul Thorsen for gross tax evasion should be dismissed.

The case should have started at the citycourt in Aarhus in the spring of 2011, but it was postponed altogether three times last year.

This year the case has been postponed three times, culminating with a victory to the defence of Poul Thorsen, when Danish High Court on Friday decided to turn the indictment against Poul Thorsen down for technical reasons.

The prosecutor, police assessor Lars Petersen, from the police of Eastern Jutland, who investigated the case of gross tax evasion, explains that the indictment was turned down, because it did not contain “the things” an indictment must contain according to the Danish law of the administration of the justice. In other words because of technical deficits in the indictment.

Most recently the tax-case was scheduled for March 29 at the citycourt in Aarhus.

In 2009, the prosecution charged former Danish autism researcher Poul Thorsen with gross tax evasion in the amount of more than 6,4 million DKK.

For this deed, the Prosecution claimed, that Poul Thorsen should be punished with prison. Poul Thorsen on the other hand – according to a news agency – claimed that he was not guilty.

The indictment stated that, during the years 2001-2005, Poul Thorsen evaded income tax on 6,430,768 DKK from fees, salary or the like.

By these illegal acts, the Danish tax authority was deprived of 3,470,020 DKK that it was owed.

Further, the defendant had been accused of intentionally evading 514,455 DKK in contributions to the labour market taxes owed to the Danish tax authority during the period from 2001 through 2005.

This indictment has now been overruled by Danish High Court. Poul Thorsen's defender is lawyer Jan Schneider from the lawfirm Tommy V. Christiansen in Aarhus.

Thorsen's name will ring familiar to many, as his autism research was sponsored substantially by the American health agency Centers for Disease Control and Prevention (CDC).

Danish daily INFORMATION in 2010 reported, that Poul Thorsen's research center Nanea at Aarhus University in 2000 received a grant of 7,8 million dollar from the American health institution Centers for Disease Control and Prevention (CDC).

The grant was administered by Danish Agency for Science, Technology and Innovation (DASTI) under the direction of Poul Thorsen.

In 2007 the project was prolonged by a new grant from CDC of 8,2 million dollar.

This is the financial context that makes the now overruled case of gross tax evasion a matter of public interest.

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Does this mean that the case was dismissed because the government attorney failed to prepare the paperwork in the correct way, or does it mean the law enforcement did not provide adequate proof to



substantiate the charge? Will they redo the charge and include the 'missing things' and refile?

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EXHIBIT 14

**PUBMED Biblio on Autism Articles for Poul Thorsen  
(Updated March 20, 2012)**

No.	Pub Date	Article	Thorsen's Affiliation
1.	Article first published online: 21 FEB 2012	1: Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand. 2012 Mar;91(3):287-300. doi: 10.1111/j.1600-0412.2011.01325.x. PubMed PMID: 22085436.	Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark
2.	Epub 2011 Sep 10	2: Abdallah MW, Larsen N, Grove J, Nørgaard-Pedersen B, Thorsen P, Mortensen EL, Hougaard DM. Amniotic fluid chemokines and autism spectrum disorders: an exploratory study utilizing a Danish Historic Birth Cohort. Brain Behav Immun.2012 Jan;26(1):170-6. Epub 2011 Sep 10. PubMed PMID: 21933705.	Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark
3.	Posted online on December 19, 2011	3: Abdallah MW, Larsen N, Grove J, Nørgaard-Pedersen B, Thorsen P, Mortensen EL, Hougaard DM. Amniotic fluid inflammatory cytokines: Potential markers of immunologic dysfunction in autism spectrum disorders. World J Biol Psychiatry.2011 Dec 19. [Epub ahead of print] PubMed PMID: 22175527.	Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark
4.	Published online 11 February 2011	4: Parner ET, Thorsen P, Dixon G, de Klerk N, Leonard H, Nassar N, Bourke J, Bower C, Glasson EJ. A comparison of autism prevalence trends in Denmark and Western Australia. J Autism Dev Disord. 2011 Dec;41(12):1601-8. PubMed PMID: 21311963.	Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark
5.	<b>Published Online First 27 June 2010</b>	5: Hvidtjørn D, Grove J, Schendel D, Schieve LA, Sværke C, Ernst E, Thorsen P. Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study. J Epidemiol Community Health. 2011 Jun;65(6):497-502. Epub 2010 Jun 27. PubMed PMID: 20584728. <i>Contributors DH, PT and JG were responsible for conception and design. DH, JG and CS conducted the statistical analyses and the interpretation of data. DH wrote the first draft of the manuscript. All authors provided critical input at all stages and critically reviewed and contributed to the final draft. PT and DH are guarantors of the study. All authors had full access to the data. Accepted 30 December 2009 Published Online First 27 June 2010</i>	Institute of Public Health at the Department of Epidemiology, University of Aarhus, Aarhus, Denmark

**PUBMED Biblio on Autism Articles for Poul Thorsen  
(Updated March 20, 2012)**

No.	Pub Date	Article	Thorsen's Affiliation
6.	Published online 23 April 2010	6: Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord. 2010 Dec;40(12):1423-30. PubMed PMID: 20414802.	Thorsen provides no affiliation. He states Atlanta, GA USA CDC employee Dr.Diana Schendel is a co-author.
7.	<b>Accepted for Publication:</b> December 3, 2009	7: Atladóttir HO, Thorsen P, Schendel DE, Østergaard L, Lemcke S, Parner ET. Association of hospitalization for infection in childhood with diagnosis of autism spectrum disorders: a Danish cohort study. Arch Pediatr Adolesc Med. 2010 May;164(5):470-7. PubMed PMID: 20439799.  <i><b>Author Contributions:</b> Dr Atladóttir had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Atladóttir, Thorsen, Schendel, Lemcke, and Parner. Acquisition of data: Atladóttir, Østergaard, and Parner. Analysis and interpretation of data: Atladóttir, Thorsen, Schendel, Østergaard, Lemcke, and Parner. Drafting of the manuscript: Atladóttir, Thorsen, Schendel, and Parner. Critical revision of the manuscript for important intellectual content: Atladóttir, Thorsen, Schendel, Østergaard, Lemcke, and Parner. Statistical analysis: Atladóttir and Parner. Obtained funding: Atladóttir, Thorsen, and Parner. Administrative, technical, and material support: Østergaard. Study supervision: Thorsen, Schendel, Østergaard, Lemcke, and Parner.</i>	Thorsen's affiliation is omitted. CDC employee Dr.Diana Schendel is a co-author.
8.	Published online 1 September 2009	8: Lauritsen MB, Jørgensen M, Madsen KM, Lemcke S, Toft S, Grove J, Schendel DE, Thorsen P. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. J Autism Dev Disord. 2010 Feb;40(2):139-48. Epub 2009 Sep 1. PubMed PMID: 19728067.	NANEA, Department of Epidemiology and Social Medicine Institute of Public Health University of Aarhus, Aarhus, Denmark
9.	Published online 5 July 2009	9: Atladóttir HO, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, Parner ET. Association of family history of autoimmune diseases and autism spectrum	NANEA, Department of Epidemiology and Department of Epidemiology, Rollins

**PUBMED Biblio on Autism Articles for Poul Thorsen  
(Updated March 20, 2012)**

No.	Pub Date	Article	Thorsen's Affiliation
		disorders. <i>Pediatrics</i> . 2009 Aug;124(2):687-94. Epub 2009 Jul 5. PubMed PMID: 19581261.	<i>School of Public Health, Emory University, Atlanta, Georgia</i>
10	Published online 13 January 2009	10: Buttenschøn HN, Lauritsen MB, El Daoud A, Hollegaard M, Jorgensen M, Tvedegaard K, Hougaard D, Børglum A, Thorsen P, Mors O. A population-based association study of glutamate decarboxylase 1 as a candidate gene for autism. <i>J Neural Transm</i> . 2009 Mar;116(3):381-8. Epub 2009 Jan 13. PubMed PMID: 19139806.	NANEA, Department of Epidemiology and Social Medicine Institute of Public Health University of Aarhus, Aarhus, Denmark
11	<b>Accepted for Publication:</b> May 29, 2008.  This article was corrected online for typographical errors on 1/26/2009.	11: Hvidtjørn D, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis. <i>Arch Pediatr Adolesc Med</i> . 2009 Jan;163(1):72-83. PubMed PMID: 19124707.	North Atlantic Neuro Epidemiology Alliances, Institute of Public Health, Department of Epidemiology, University of Aarhus, Århus, Denmark and Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia
12	<b>Accepted for Publication:</b> May 8, 2008	12: Parner ET, Schendel DE, Thorsen P. Autism prevalence trends over time in Denmark: changes in prevalence and age at diagnosis. <i>Arch Pediatr Adolesc Med</i> . 2008 Dec;162(12):1150-6. PubMed PMID: 19047542.  <b>Author Contributions:</b> Dr Parner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. <i>Study concept and design:</i> Parner, Schendel, and Thorsen. <i>Acquisition of data:</i> Parner. <i>Analysis and interpretation of data:</i> Parner, Schendel, and Thorsen. <i>Drafting of the manuscript:</i> Parner. <i>Critical revision of the manuscript for important intellectual content:</i> Parner, Schendel, and Thorsen. <i>Statistical analysis:</i> Parner. <i>Obtained funding:</i> Schendel and Thorsen. <i>Administrative, technical, and material support:</i> Schendel and Thorsen. <b>Financial Disclosure:</b> None reported. <b>Disclaimer:</b> The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for	North Atlantic Neuro Epidemiology Alliances, Department of Epidemiology, Institute of Public Health, University of Aarhus, Aarhus, Denmark and Department of Epidemiology, Rollins School of Public Health, Emory University Atlanta, Georgia

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No.	Pub Date	Article	Thorsen's Affiliation
		Disease Control and Prevention.	
13	Article first published online: 10 SEP 2008	13: Maimburg RD, Vaeth M, Schendel DE, Bech BH, Olsen J, Thorsen P. Neonatal jaundice: a risk factor for infantile autism? <i>Paediatr Perinat Epidemiol.</i> 2008 Nov;22(6):562-8. PubMed PMID: 19000294.	Departments of Epidemiology Institute of Public Health, University of Aarhus, Aarhus
14	March 2007	14: Atladóttir HO, Parner ET, Schendel D, Dalsgaard S, Thomsen PH, Thorsen P. Variation in incidence of neurodevelopmental disorders with season of birth. <i>Epidemiology.</i> 2007 Mar;18(2):240-5. PubMed PMID: 17202868.	NANEA, Department of Epidemiology, Institute of Public Health, University of Aarhus, Aarhus, Denmark
15	February 2007 <b>Accepted for Publication:</b> August 23, 2006	15: Atladóttir HO, Parner ET, Schendel D, Dalsgaard S, Thomsen PH, Thorsen P. Time trends in reported diagnoses of childhood neuropsychiatric disorders: a Danish cohort study. <i>Arch Pediatr Adolesc Med.</i> 2007 Feb;161(2):193-8. PubMed PMID: 17283306.	North Atlantic Neuro-Epidemiology Alliances at Department of Epidemiology Institute of Public Health, University of Aarhus, Aarhus, Denmark
16	Published online 4 August 2005	16: Skogstrand K, Thorsen P, Nørgaard-Pedersen B, Schendel DE, Sørensen LC, Hougaard DM. Simultaneous measurement of 25 inflammatory markers and neurotrophins in neonatal dried blood spots by immunoassay with xMAP technology. <i>Clin Chem.</i> 2005 Oct;51(10):1854-66. Epub 2005 Aug 4. PubMed PMID: 16081507.	<i>NANEA at Department of Epidemiology and Social Medicine, Aarhus University, Aarhus, Denmark</i>
17	Published 15 May 2005  Received February 6, 2004. Accepted August 11, 2004	17: Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. <i>Am J Epidemiol.</i> 2005 May 15;161(10):916-25; discussion 926-8. PubMed PMID: 15870155. <i>The National Centre for Register-based Research is funded by the Danish National Research Foundation. The study was partially supported under a cooperative agreement from the Centers for Disease Control and Prevention, Atlanta, Georgia; by a grant from the March of Dimes Birth Defects Foundation, New York, New York; by the Stanley Medical Research Institute; and by National Institute of Mental Health grant MH53188.</i>	North Atlantic Neuro-Epidemiology Alliances, Department of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark  CDC employee Dr.Diana Schendel is a co-author

**PUBMED Biblio on Autism Articles for Poul Thorsen  
(Updated March 20, 2012)**

No.	Pub Date	Article	Thorsen's Affiliation
18	Published 13 September 2004	18: 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 registry-data]. Ugeskr Laeger. 2004 Sep 13;166(38):3291-3. Danish. PubMed PMID: 15496004.	Aarhus Universitet, Institut for Epidemiologi og Socialmedicin, Center for Epidemiologisk Grundforskning
19	Published 11 September 2003	19: 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 Sep;112(3 Pt 1):604-6. PubMed PMID: 12949291. <i>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. (All from CDC)</i>	Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Aarhus, Denmark
20	Published December 2, 2002	20: Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, Olsen J, Melbye M. [MMR vaccination and autism--a population-based follow-up study]. Ugeskr Laeger. 2002 Dec 2;164(49):5741-4. Danish. PubMed PMID: 12523209.	Center for Epidemiologisk Grundforskning, Institut for Epidemiologi og Socialmedicin, Aarhus Universitet
21	Published November 7, 2002	21: 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 Nov 7;347(19):1477-82. PubMed PMID: 12421889. Supported by grants from the Danish National Research Foundation; the National Vaccine Program Office and National Immunization Program, Centers for Disease Control and Prevention; and the National Alliance for Autism	Danish Epidemiology Science Center, Department of Epidemiology and Social Medicine, Århus, Denmark  CDC employee Dr.Diana Schendel is a co-author.



**PUBMED Biblio on Autism Articles for Poul Thorsen  
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No.	Pub Date	Article	Thorsen's Affiliation
		<p>Research.</p> <p><i>We are indebted to Susanne Toft and Meta Jørgensen for the abstraction and review of medical records and to Catherine Rice and Nancy Dornberg for assistance with the validity substudy. <b>Source Information</b> From the Danish Epidemiology Science Center, Department of Epidemiology and Social Medicine, Århus, Denmark (K.M.M., M.V., P.T., J.O.); the Danish Epidemiology Science Center, Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark (A.H., J.W., M.M.); and the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta (D.S.).</i></p>	

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## iPSYCH project to study five specific mental disorders

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Is it possible to prevent the development of schizophrenia? Can certain patients develop autism if they carry a specific gene and have been exposed to a viral fetal infection? Should all ADHD patients take the same type of medication?

This unique research project will try to answer these questions. The project is based at Aarhus University and will be known as 'The Lundbeck Foundation's Initiative for Integrative Psychiatric Research' (iPSYCH). The grant of DKK 121m from the Lundbeck Foundation is the largest grant ever awarded to Danish psychiatric research.

- We will investigate why some people develop mental disorders. We will identify biological disease mechanisms, and we also intend to provide the basis for better treatment and prevention, says Dr. B-rglum, Professor of Medical Genetics at Aarhus University and Scientific Director of the research project.

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### The many faces of psychiatry

The project will study five specific mental disorders: schizophrenia, manic depression, depression, autism and ADHD. All disorders are associated with major human and societal costs all over the world. The new thing is that researchers will study these disorders from many different angles, ranging from genes and cells to population studies, from fetus to adult, from cause to symptoms of the disorder, and this knowledge will be combined in new ways across scientific fields.

- People suffering from a mental disorder such as schizophrenia may have very different lives: a family life with children and a job - or a life characterized by chronic disease and homelessness. The disorders do not affect all patients in exactly the same way. We do not know why, but we do know that our current treatment methods are far from optimal because we need more knowledge about the causes behind the disorders, but also about the differences in the development, says Dr. B-rglum.

- Our main goal is to identify the causes of these disorders by studying the interplay between genetic and environmental factors and thereby find new targets for treatment. The perspective is to offer better and individualized treatment, providing a better life for each individual patient with the disorder - and perhaps even ways to prevent the development of the disorder in some cases, he says.

Professor Mikael R-rth, Chairman of the Board of Trustees of the Lundbeck Foundation, is pleased with the research opportunities that the new grant will offer:

- Mental disorders are determined by a combination of genetic and psycho-social factors. The research project will combine unique Danish registers and biobanks and is expected to pave the way for better treatment in the future, says Dr. R-rth.

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EXHIBIT 16

# The Lundbeck Foundation Centre for Interventional Research in Radiation Oncology

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## Researchers

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### *Researchers in CIRRO*

#### **Senior Scientists**

1. Alsner, Jan. Associate professor, AUH. WP01 leader. WP coordinator.
2. Andersen Claus. Associate professor, Risø-DTU. WP08 leader.
3. Andreassen, Nicolaj. MD PhD, AUH.
4. Bangsgaard, Jens-Peter. Medical physicist, RH. CAK.
5. Bassler, Niels. Associate professor, AU.
6. Behrens, Claus. Physicist PhD, Herlev.
7. Bentzen, Lise. MD PhD, AUH.
8. Brink, Carsten. Associate professor, OUH. WP05 leader.
9. Busk, Morten. Senior scientist PhD, AUH
10. Carl, Jesper. Chief physicist, Aalborg. WP07 leader, CAK
11. Engelholm, Svend Aage. Professor MD, RH. IP11 coordinator.
12. Eriksen, Jesper Grau. MD PhD, OUH
13. Fledelius, Walther. Postdoc, AUH
14. Grau, Cai. Professor MD, AUH. Scientific coordinator. CAK
15. Hansen, Olfred. MD PhD, OUH. IP02 coordinator. CAK
16. Havsteen, Hanne. MD PhD, Herlev. IP13 coordinator
17. Helt-Hansen, Jakob. Senior scientist, Risø-DTU
18. Høyer, Morten. Associate professor MD, AUH. IP06 and IP08 coordinator.
19. Jakobsen, Anders. Professor MD, Vejle. IP09 coordinator. CAK
20. Johansen, Jørgen. MD PhD, OUH
21. Korreman, Stine. Director of Physics Research, RH. WP06 leader. CAK.
22. Kristensen, Brian. Chief physicist, Herlev. CAK
23. Larsen, Rasmus. Professor, DTU.
24. Laursen, Louise Vagner. Academic coordinator, post doc. AUH
25. Lauritzen, Bent. Head of programme, Risø-DTU. CAK
26. Lindegaard, Jacob. Associate professor MD, AUH. IP10 and IP 12 coordinator.
27. Lühr, Armin. Postdoc, AU.
28. Muren, Ludvig. Associate professor, AUH
29. Nielsen, Thomas. Postdoc, AUH
30. Nordsmark, Marianne. MD PhD, AUH. WP02 leader and IP05 coordinator.
31. Nørrevang, Ole. Chief physicist, AUH

#### **Jump to:**

- Senior Scientists
- PhD Students

32. Offersen, Birgitte. MD PhD, AUH. IP03 coordinator.
33. Overgaard, Jens. Professor MD, AUH. Director. IP01 coordinator
34. Pedersen, Erik Morre. MD PhD, AUH
35. Petersen, Jørgen. Senior scientist PhD, AUH.
36. Petersen, Peter Meidahl. MD PhD, RH. IP08 leader.
37. Poulsen, Per Rugaard. Senior scientist PhD, AUH.
38. Skogholt, Peter. Medical physicist, Vejle Sygehus.
39. Sørensen, Brita Singers. Postdoc, AUH.
40. Sørensen, Thomas Sangild. Associate professor, AU. WP03 leader.
41. Specht, Lena. Professor MD, RH. IP04 coordinator.
42. Tanderup, Kari. Postdoc, AUH. WP coordinator.
43. Vogelius, Ivan. Postdoc, RH. WP09 leader.
44. Wojdacz, Tomasz. Postdoc, AU.
45. Østergaard, Leif. Professor, AUH. WP04 leader.

## PhD students

### Jump to:

1. Appelt, Ane: Evaluation of dose plan quality with focus on prediction of side-effects following radiotherapy of lung and rectum [Evaluering af dosisplankvalitet med fokus på prædiktion af bivirkninger ved strålebehandling af lunge og rectum]. University of Southern Denmark (enrolled 2010).
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## As the agitator came to the University

Research Nanea should have been the world's best. Today slogans died, the group is dissolved, and the head of the whole thing is bolted to the U.S. dogged by suspicions of fraud for millions. And funkisvillaen who harbored the dream, stands empty and abandoned



Abandoned. A little mess in an abandoned villa in Aarhus Vest is the last physical remnants that remain of what was to be the world's best research. Photo: Sigrid Nygaard

By: SALLY MAJA FUNCH  
12th March 2010 | [About this Article](#)

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Keywords: labor , public health , researchers , research , lifestyle , media , tax evasion , spin , university , economics

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Locations: Copenhagen , U.S.

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"I'm ready to kill to come forward."



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The phrase strikes a nerve in Anja when she hears his boss talking about the ambition that drives his career. For one thing he is joking, but jest and earnest as we know, complementary, and Anja have seen and heard it all before. For many months she has worked in the research Nanea at Aarhus University. During that time she has seen his boss when he explains that he

would sacrifice a friendship for a position, and that he also does not care whether there are better candidates if he comes first. Anja has seen what happens when a new article is ready for publication, and the researchers determined the order of names in the article byline.

Gradually, by Anja also that she did not thrive in the game, and that her career should have a new twist. However she does not know that also the whole Nanea heading for doom.



**Den Mindst Ringe i  
din indbakke**

TILMELD NYHEDSBREV I DAG

The tale begins long before the year 2000. Here are launching a lecturer, a research project with a range that matches any vision for the new millennium. Through several years, researchers in the North Atlantic Neuro-Epidemiology Alliances examine data in large files and thousands of children to find correlations between pregnant women's lifestyle and children's abilities in later life. Data is probably the world's largest, and several other groundbreaking projects to be launched around the first. The same format has the project creates. Poul Thorsen's him with the high grin. That's him with millions from the U.S. , making the research possible, and the life of a luxury travel for employees. That's him with the plans and the panels that describe how Nanea is world domination, and it is he who causes the device to dance to his pipe, even when they sense that something is wrong.

For Poul Thorsen is also the contractor. A few months after the interview with Anja, he directs the University of Aarhus into what looks like a historical scandal about fraudulent research for more than 10 million dollars, which he himself takes the lead as the academic response to business Stein Bagger or Tvind cult Amdi.

On the border for spring 2009 are growing suspicions in the upper layers of the administration at the University of Aarhus: Something is wrong with the unit at the Department of Public Health. Nanea do not have the funds available as the project leader suggests. Poul Thorsen is raised. The year before he went to Atlanta, where he manages the research. But in March, exactly a year since the exile lecturer finally caught on his unit. While the university digs into the murky circumstances surrounding the funding, he said in his resignation. In May, the University of Aarhus to the police, but not until February of this year is the scandal in the Danish media: missing millions in the box at Aarhus University, and it looks like a case of fraud. Someone has falsified signatures on declarations of funding for a research unit at the university. Perhaps there is money that has disappeared, and the unit's star has received double salaries as full-time employee at both Aarhus University and a university in Atlanta.

Poul Thorsen has not yet been charged with the false signatures and black holes. But suspicion is sticking to the man who was NANEA father, leader and self-willed ruler. In the center of Aarhus prepares Østjyllands Police criminal proceedings. And while the police gather material and statements from witnesses, a similar soul-searching process in motion elsewhere in the city:

"We started in Nanea. This promising research. And now there is something called Nanea more. It is one man's profit, there came something really good research and stand. But it is also with him, the house of cards falls, because he has the flaws he has. Why did not we react? "

It's Lise, who ponders. Just like Anja, she was along for the ride from glory to fall. Together with another employee, Toke, they agreed to tell their version of the shipwreck at Aarhus University and the road thither. They make up because the story of Nanea just like other good parables beyond itself and the functionalist Paludan Müller Road in the north of Aarhus, where the enclave lived. It is also the story of an academic world where competition for money, prestige and the right to investigate tougher every year.

### **The golden child**

Anja remembers his first day at Nanea. High and low, from secretaries to

senior, the group lined up in a row, sharing hugs out to the new girl when she starts a few years into the life of the project. Lise also remembers the mood. With the jelly in the knees she stands up in front of his boss to point out a few poorly thought-out details. But all nerves are put to shame, because his arms are just as open when it comes to new ideas and new employees.

"You should see options! It was Poul Thorsen's slogan, and I can see that he created an alternative research. It built on the principle that everyone was equal worth and had something to offer here," she says.

One thing is certain, Nanea is unique from the start. This is due to two factors, both of which give the device a status that most academic environments only dream about. First, NANEAs plating. The project's name is on a grant of nearly eight million dollars. Gold vein is the American health care institution, CDC Atlanta, and in the years to come, float another eight million dollars to Nanea. The second factor is the scale. Denmark is a register-country. We sit on a knowledge not available to the money men *over there*, and the knowledge, Poul Thorsen access. Based on databases that are full of records of the pregnant woman's lifestyle, work NANEAs researchers to map how even tiny amounts of alcohol affect children's intelligence later in life. They examine the reasons for including autism and cerebral palsy on the basis of the figures in other registers. The total material is so extensive that several NANEAs projects is the deepest in the world of their kind.

The size also makes the group grows beyond the scope of the parent department of Epidemiology at University Park in Aarhus. It will have its own headquarters in a large, square house a kilometer away. From headquarters in Paludan Müller way the device continues to distance itself from the rest of the academic environment.

### **The family**

One trait Nanea differs from the rest of the university, and it springs to mind immediately. In the first years of the employees live in a world of glitz and pampering. "We run in a huge Mercedes! Is the watchword, and it's true. Every time a scientist travels into the country to gather data, it is in business class, says Anja. Lise says that the Danes are visiting in Atlanta, where they are impressed when a limousine rolls up in front of the hotel door to take them to meetings with the CDC. Delicious dinners, expensive brands of alcohol and stay in luxury *get-aways* as Denmark's castles are on the program when the traffic goes the other way and money the men from the USA visiting Denmark.

At the same time keeping the group together in a rare degree. Nanea celebrations. Summer festivals, winter celebrations, Christmas celebrations, there is always an occasion, or else there are seminars. Anja call them energy meetings. Toke and Lisa remember their formal name, *off-site*. Here, the employees go away a few days. They go in groups and make presentations, where they share their work with each other. But first and foremost share the vision of Nanea.

Anja still see the head of it. The white canvas is stretched out behind him. Models and strategies are drawn with NANEAs colors and logo of the power point slides, he clicks through. Poul Thorsen speaks. He talks about the future that belongs Nanea. He talks about becoming the world's top research institution, the brightest in his field. And he talks about how Nanea reach the goal together.

"We should be *committed*. It was Poul Thorsen's words, and it seemed a long way down the road. I committed myself to it," says Lise.

"We should always define who we were. We were *naneanere*. There was Nanea on the mailbox to our house. We had our own logo and our own little things. When a graduate was finished, she got a Nanea-belt with a buckle Nanea-and small-Nanea things we could have on the body "remembers Anja.

NANEA are a family. That they call themselves, and the family has a chronicle. For although the group has grown out of the Department of Epidemiology, the two now quite different. *They* are jealous of our resources while *we* are special because we have them. They are bureaucrats, while we're loose and large. In the middle of the chronicle is NANEA father. Poul Thorsen has created the family, and his charisma binds the group together.

"He could do everything, and he could at least make it good for people. He cried and laughed out loud so we could hear him all over. There was a bit of hopping around for him when he was in the house. Poul Thorsen - that's him, we would like to dance with, "says Anja.

### **The entrepreneurial university**

A new era has come to the Danish universities and Nanea is the example of the time.

In the old days people sat hunched over their microscopes or stacks of thick books. Solid walls protected them against the world's hullabaloo, while the overall puzzle of nature's mysteries. Often nobody knew what the new knowledge should be used. Jens Christian Skou won the last Nobel Prize in Denmark in 1997, but physiologist published the first knowledge of his discoveries in 1957.

Today, the ivory tower collapsed. Claus Emmeche director of the Center for Philosophy of Nature and Science Studies at the Niels Bohr Institute. He is also among the front runners in the debate on how Denmark's intellectual strongholds controlled. Claus Emmeche not know what's been going on in the environment around Nanea. In return, he knows what it takes to succeed in a new academic landscape, and running heads as Poul Thorsen quickly from researchers Jens Christian Skou.

In december announced an international expert panel's evaluation of the new University from 2003 and mergers in 2007, and therefore the debate on universities to date. The very last of the two events mark the result Claus Emmeche a milestone in terms of research in Denmark. This year breaks the politicians with the classical division of labor between research types. Until then, the research industry for its own money and to earn more. Sector Research gets its tasks and its funding from the ministries. Only universities are free to do research for research's sake, without loosing in. For 2007, not only the year when Aarhus School of Business and Aarhus University becomes one. At the same time, the universities and a number of sector research institutions.

"Now they have also taken over the government research institutions challenge. They must ensure that the ministries will continue to think it worthwhile to finance their research. This means that they spend a large proportion of working to justify itself by continually making new contracts with customers for research, "explains Claus Emmeche.

"The entrepreneurial university ', he calls a new era in which the skilful researcher not only is he who with hard work peels layers of human ignorance. Here, "winner of the researcher who is good to appear dynamic and good for networking. It is he who can brand themselves and their research and passion to be entrepreneurial and scrape the money together ", says associate professor.



For the community will see the proceeds of the deposit and more every year. And while the base funding for the fumbling basic shrinking by two percent each time the year changes, increases the risk that competition culture negative side effects really turn out in Denmark academic environments.

### **Tax evasion**

The unit begins Nanea decay to ravage. One day Anja gets a letter in the mail. It is from TAX, and says that SKAT has received an anonymous tip that among other concerns Anja. She is one of several employees who receive public money, which she is entitled.

Anja is employed in a wage subsidy scheme. More precisely, given Anja salary and an amount that Poul Thorsen put on top of each month, so she ends up at the right salary for his full-time work. It is not legal. On the other hand, it is a condition of her employment. The letters give turmoil. There are several who have to pay money back. They confront Poul Thorsen with it.

"It's really embarrassing for you", says Anja head and sticks a letter, dated back to the beginning of her employment. It says that she is compensated for expenses for travel and equipment, and the meaning is that Anja gives the letter to the Tax and get rid of his bill.

Tax case shows two things. One is that the economy is lagging so much in Nanea that several employees paid illegally. The second is that it is hopeless to talk with the boss about the problem. Poul Thorsen is' wool in the mouth "when he demanded an answer that explains Toke. All notes that there are firewalls between the man on the floor and NANEA economy. Researchers can not get to know if it's millions from CDC or funds from other investors who pay their salaries. Nobody can get to know where the money is from and whether there is enough to make each project completed.

In return, the boss does nothing to diminish the expectations for the future.

"You can say a lot, but he was good to get ideas, and there came more and more," says Anja, who also explains that rhetoric creates an elaborate spin, which diverts attention from the wool of Poul Thorsen's answers and motivates everyone to to continue.

Poul Thorsen told his unit for talented new colleagues who can start tomorrow, if only naneanerne tackles and helping to raise funds home. He draws in air and on its posters and talks about the *blood spots* and other projects which research can be extended with when the power returns.

"You must put in the pot for the common good. So we draw twice as much next year," encourages Poul Thorsen, and Lisa finds that Nanea liver, the commander directs.

"It makes you do in a family. You stretch out for each other. "

But power is not in Nanea. In 2008, Poul Thorsen packs his bags and move to Atlanta. Toke perceive it as if he escapes. The head of the whole thing leaves scientists in the big house and in an economic quagmire that only he is responsible. After New Year says Poul Thorsen his post. Nanea door with his father, while scandal gathers around him.

### **Seduced**

At Frederiksberg holds Danish Magisterforening to. There are a lot of university research scientists organized and Jens Vraa-Jensen is a consultant for some of them. Fudge Riet at Aarhus University does not

surprise him. Economic antics such as Anja's creative compensation packages are usually stopped by the local union representatives in the universities, before DM even hear about them. Yet Jens Vraa-Jensen faced 10 questions on illegal wage subsidy schemes in recent years and the reason is clear, according to him. It is "rather unique" in the Danish labor that employees of the university community must come to work with their own salary in the backpack - and that they smoke, if the maneuver fails. Last year, said the Science Faculty in Copenhagen farewell to 70 employees due to downsizing. Reductions give a hint with a towbar on the properties that characterize the talented staff at Danish universities:

"The redundancies hit only those who were funded by permanent appropriations, and in principle should have the safest work, while those on the external projects went free. So some researchers begin to look for ways they can improve their economy, "notes Jens Vraa-Jensen.

The analysis resonate at the Center for Philosophy of Nature and Science Studies. Here attacking Claus Emmeche the university system that celebrates fundraiser and builder rather than the conscientious specialist. The sun shines on it, once you have proven that he can raise large funds, which keeps alive the flame of hope that there will be more. He is allowed to be in peace, and this limits the entrepreneurial university 'certain Stein Bagger types to commit fraud and scams. "

Nanea is dead. But projects will be finished within a new framework, and even a job wriggling in the old unit. Ex-Naneans have to understand what really happened. For Toke the matter is clear: He worked under a great manager with an equally incomprehensible morality, but the head was allowed to stretch out into a world that gave way to his inclinations.

"We have created a highly competitive system, where large sums of money goes to individuals with large groups of scientists and favors in a way such people. If you can sell yourself, you fling yourself in this system. If you actually are unscrupulous and not clouds criminal acts, you can at least for a time enjoy yourself, so I do not think it is the latter case, we see '.

Poul Thorsen was the new age man. He "will have its arm movements," and he "always cursing and swearing all over the bureaucracy," said Lise. But the ideas were good, and therefore she is not that old tub was rotten before it sank. The surprise Lise would like to save others.

"For me it is a seduction story. An agitator things. The university pays tribute to punctiliousness in research. We should do everything exactly alike, and we had to meet the most stringent research criteria. It takes a long time before you realize that someone is playing the game on a completely different way. "

#### **PS**

The story of Nanea based on conversations with Toke, Lise and Anja on what they have each experienced their time in Nanea. East Jutland Police, Aarhus University and Research and Innovation has helped with background knowledge. Toke, Lise and Anja are fictional names. Information knows their real identity.

Information has contacted Poul Thorsen through his Danish lawyer Jan Schneider. Poul Thorsen did not want to participate in the article, but Jan Schneider maintains that his client is innocent.

#### **NANEA Rise and Fall**

2000 Nanea created with an appropriation of \$ 7.8 million from the U.S. health care Centers for Disease Control and Prevention ( CDC ). Grant administered by the Research and Innovation under the direction of Poul

Thorsen.

2007 project is extended for a further grant from the CDC at \$ 8.2 million.

2008 Poul Thorsen moved to Atlanta, but is still scientific and administrative head of Nanea.

Winter 2008-2009 AU discovers that there are no funds available for research, which Nanea have used. Poul Thorsen assures that there is money coming from the U.S. and provides declarations of grants as documentation.

March 2009 Poul Thorsen resigns his position at Aarhus University. Nanea disbanded, but the projects will continue under new management.

Spring 2009 University of Aarhus discovers that three letters of grants from the CDC apparently falsified, just as the CDC does not acknowledge a letter on an outstanding amount of NANEA first appropriation. In all, the fake signatures of a sum of nearly two million dollars.

May 2009 Science, Technology and Innovation Council lodges a police report. The notification is not directed against any named person.

Fall 2009 University of Aarhus discovers that Poul Thorsen has maintained a dual appointment as associate professor in Denmark and a professor at Emory University in Atlanta and University of Aarhus has not approved.

January 2010 University of Aarhus director Jorgen Jorgensen denounces Poul Thorsen in a message to Nanea-project partners. The message also mentions fraud case.

February 2010 Savannah Morning News takes up the case and the other media will follow.

March 2010 Østjyllands Police investigators continue to raise a charge against the key person.

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February 2010: Savannah Morning News takes up the case and the other media will follow.

March 2010: Østjyllands Police investigators continue to raise a charge against the key person.

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## Da agitatoren kom til universitetet

Forskningsenheden Nanea skulle have været verdens bedste. I dag er slagordene døde, gruppen er opløst, og chefen for det hele er stukket af til USA forfulgt af mistanker om svindel for millioner. Og funkisvillaen, der husede drømmen, står tom og forladt



Forladt. Lidt rod i en forladt villa i Århus Vest er de sidste fysiske rester, der er tilbage af det, der skulle være verdens bedste forskningsmiljø Foto: Sigrid Nygaard

Af: SANNE MAJA FUNCH  
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### Opslag til denne artikel

Emneord: arbejdsmarked, folkesundhed, forskere , forskning , livsstil, medier, skattesnyd, spin, universiteter, økonomi

Organisationer: Aarhus Universitet, SKAT

Steder: København, USA

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»Jeg er klar til at slå ihjel for at komme frem«.



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Sætningen rammer en nerve i Anja, da hun hører sin chef fortælle om den ambition, der driver hans karriere. For nok taler han i spøg, men spøg og alvor er som bekendt komplementære størrelser, og Anja har set og hørt det hele før. I mange måneder har hun arbejdet i forskningsenheden Nanea på Aarhus Universitet. I den tid har hun oplevet sin chef,

når han forklarer, at han gerne ofrer et venskab for en stilling, og at han i øvrigt er ligeglad med, om der findes bedre kandidater, hvis han selv kommer først. Anja har set, hvad der sker, når en ny artikel er klar til publikation, og forskerne slås om rækkefølgen af navne i artiklens byline.

Efterhånden ved Anja også, at hun ikke trives i det spil, og at hendes karriere skal have en ny drejning. Derimod ved hun ikke, at også hele Nanea styrer mod undergang.



**Den Mindst Ringe i  
din indbakke**

TILMELD NYHEDSBREV I DAG

Eventyret starter lang tid før, i år 2000. Her søsætter en lektor et forskningsprojekt med en rækkevidde, der matcher enhver vision for det ny årtusinde. Gennem adskillige år skal forskerne i North Atlantic Neuro-Epidemiology Alliances undersøge data i store registre og tusinder af børn for at finde sammenhænge mellem gravide kvinders livsstil og børnenes evner senere i livet. Datamaterialet er formentlig verdens største, og flere andre banebrydende projekter sættes i gang omkring det første. Samme format har projekternes skaber. Poul Thorsen er ham med det høje grin. Det er ham med millionerne fra USA, der gør forskningen mulig og livet til en luksusrejse for de ansatte. Det er ham med planerne og plancherne, der beskriver, hvordan Nanea tager verdensherredømmet, og det er ham, der får enheden til at danse efter sin pibe, selv da de mærker, at noget er galt.

For Poul Thorsen er også entreprenøren. Få måneder efter samtalen med Anja styrer han Aarhus Universitet ind i det, der ligner en historisk skandale om svindel med forskningsmidler for mere end 10 millioner kroner, hvor han selv tager hovedrollen som den akademiske verdens svar på erhvervslivets Stein Bagger eller Tvind-kultens Amdi.

På grænsen til foråret 2009 vokser en mistanke i de øverste administrative lag på Aarhus Universitet: Noget er galt i enheden ved Institut for Folkesundhed. Nanea har ikke de midler til rådighed, som projektets leder giver indtryk af. Poul Thorsen er rejst. Året før tog han til Atlanta, hvorfra han styrer forskningen. Men i marts måned for præcis et år siden slipper eksil-pektoren endeligt grebet om sin enhed. Mens universitetet graver i de dunkle forhold omkring fundingen, siger han sin stilling op. I maj indgiver Aarhus Universitet en anmeldelse til politiet, men først i februar i år springer skandalen i de danske medier: Der mangler flere millioner i kassen på Aarhus Universitet, og det ligner en sag om bedrageri. Nogen har sat forfalskede signaturer på tilkendegivelser om bevillinger til en forskningsenhed ved universitetet. Måske er der penge, som er forsvundet, og enhedens stjerne har modtaget dobbelt løn som fuldtidsansat ved både Aarhus Universitet og et universitet i Atlanta.

Poul Thorsen er endnu ikke sigtet for de falske underskrifter og de sorte huller. Men mistanken klæber til den mand, der var Naneas fader, leder og egenrådige hersker. I centrum af Århus forbereder Østjyllands Politi en straffesag. Og mens politiet samler materiale og afhører vidner, er en tilsvarende ransagelsesproces i gang andre steder i byen:

»Vi startede i Nanea. Den her lovende forskningsinstitution. Og nu er der ikke noget, der hedder Nanea mere. Det er én mands fortjeneste, at der kom noget virkelig god forskning op og stå. Men det er også med ham, korthuset falder, fordi han har de brister, som han har. Hvorfor reagerede vi ikke?«

Det er Lise, som grubler. Lige som Anja var hun med på turen fra storhed til fald. Sammen med endnu en medarbejder, Toke, har de sagt ja til at fortælle deres version af skibbruddet på Aarhus Universitet og vejen derhen. De stiller op, fordi fortællingen om Nanea lige som andre gode lignelser rækker ud over sig selv og den funkisvilla på Paludan Müllers Vej i Århus' nordlige bydel, hvor enklaven holdt til. Den er samtidig historien om en akademisk verden, hvor konkurrencen om penge, prestige og retten til at forske skærpes år for år.

### **Det gyldne barn**

Anja kan huske sin første dag på Nanea. Høj som lav, fra sekretær til seniorforsker, er gruppen linet op på række og deler knus ud til den nye

pige, da hun starter et par år inde i projektets levetid. Lise husker også stemningen. Med gele i knæene stiller hun sig op foran sin chef for at pege på et par dårligt tænkte detaljer. Men al nervøsitet bliver gjort til skamme, for armene er præcis lige så åbne, når det gælder nye ideer som nye medarbejdere.

»Man skal se muligheder! Det var Poul Thorsens slogan, og jeg kan godt se, at han skabte et alternativt forskningsmiljø. Det byggede på et princip om, at alle var lige meget værd og havde noget at byde ind med«, siger hun.

Ét er sikkert, Nanea er unikt fra starten. Det skyldes to faktorer, der begge giver enheden en status, de fleste akademiske miljøer kun drømmer om. For det første er Nanea forgyldt. Projektets navn står på en bevilling på knap otte millioner dollar. Guldåren er den amerikanske sundhedsinstitution, CDC fra Atlanta, og i årene, der kommer, flyder endnu otte millioner dollar til Nanea. Den anden faktor er programmets omfang. Danmark er et register-land. Vi sidder på en viden, der ikke findes hos pengemændene *over there*, og den viden har Poul Thorsen adgang til. Med udgangspunkt i databaser, der bugner af optegnelser over gravide kvinders livsstil, arbejder Naneas forskere med at kortlægge, hvordan selv bittesmå mængder alkohol påvirker børns intelligens senere i livet. De undersøger årsagerne til blandt andet autisme og spastiske lammelser på baggrund af tallene i andre registre. Det samlede materiale er så omfattende, at flere af Naneas projekter er de grundigste i verden af deres art.

Størrelsen gør også, at gruppen vokser ud over rammerne på moderafdelingen for Epidemiologi i universitetsparken i Århus. Den får sit eget hovedkvarter i en stor og firkantet villa en lille kilometer derfra. Fra domicilet på Paludan Müllers Vej fortsætter enheden med at lægge afstand til det øvrige akademiske miljø.

### Familien

Ét karaktertræk adskiller Nanea fra resten af universitetet, og det springer i øjnene med det samme. I de første år lever medarbejderne i et univers af glitter og forkælelse. »Vi kører i en kæmpestor Mercedes!« er parolen, og det er ganske vist. Hver gang en forsker rejser ud i landet for at samle data, foregår turen på business class, siger Anja. Lise fortæller, at danskerne tager på besøg i Atlanta, hvor de duperes, da en limousine ruller op foran hotellets dør for at køre dem til møderne med CDC. Lækre middage, spiritus med dyre etiketter og ophold på luksuriøse *get-aways* som Danmarks slotte er på programmet, når trafikken går den anden vej, og pengemændene fra USA besøger Danmark.

Samtidig holder gruppen sammen i en sjælden grad. Nanea fester. Sommerfester, vinterfester, julefester, der er altid en anledning, og ellers er der seminarerne. Anja kalder dem energi-møder. Toke og Lise husker deres formelle navn, *off-site*. Her tager medarbejderne afsted et par dage. De går i grupper og holder oplæg, hvor de deler deres arbejde med hinanden. Men først og fremmest deler de visionen om Nanea.

Anja ser stadig chefen for sig. Det hvide lærred er spændt ud bag ham. Modeller og strategier er tegnet med Naneas farver og logo i de power point-slides, han klikker sig igennem. Poul Thorsen taler. Han taler om fremtiden, som tilhører Nanea. Han taler om at blive verdens bedste forskningsinstitution, den dygtigste på sit felt. Og han taler om, hvordan Nanea når målet sammen.

»Vi skulle være *committed*. Det var Poul Thorsens ord, og det virkede et langt stykke hen ad vejen. Jeg engagerede mig i det,« siger Lise.

»Vi skulle hele tiden definere, hvem vi var. Vi var jo *naneanere*. Der stod

Nanea på postkassen til vores hus. Vi havde vores eget logo og vores egne små ting. Når en ph.d. blev færdig, fik hun et Nanea-bælte med et Nanea-bæltespænde og små Nanea-ting, vi kunne have på blusen«, husker Anja.

Nanea er en familie. Det kalder de sig selv, og familien har en krønike. For selv om gruppen er vokset ud af Afdeling for Epidemiologi, er de to i dag helt forskellige. De er jaloux på vores midler, mens vi er særlige, fordi vi har dem. De er bureaukrater, mens vi er loose og large. Midt i krøniken står Naneas fader. Poul Thorsen har skabt familien, og hans karisma kitter gruppen sammen.

»Han kunne det hele, og han kunne i hvert fald gøre det godt for folk. Han råbte højt og grinte højt, så vi kunne høre ham over alt. Der var lidt en hoppen rundt efter ham, når han var i huset. Poul Thorsen - det er ham, vi gerne vil danse med«, forklarer Anja.

### **Det entreprenante universitet**

En ny tid er kommet til de danske universiteter, og Nanea er eksemplet på den tid.

I gamle dage sad forskerne bøjet over deres mikroskoper eller stakkene af tykke bøger. Solide mure skærmede dem mod verdens hurlumhej, mens de samlede puslespillet om naturens gåder. Ofte vidste ingen, hvad den nye viden skulle bruges til. Jens Christian Skou vandt den seneste nobelpris til Danmark i 1997, men fysiologen publicerede den første viden om sine opdagelser i 1957.

I dag er elfenbenstårnet styrtet i grus. Claus Emmeche er leder af Center for Naturfilosofi og Videnskabsstudier ved Niels Bohr Institutet. Han er også blandt frontløberne i debatten om, hvordan Danmarks intellektuelle højborges styres. Claus Emmeche ved ikke, hvad der er foregået i miljøet omkring Nanea. Til gengæld ved han, hvad det kræver at få succes i et nyt akademisk landskab, og der løber ledere som Poul Thorsen hurtigt fra forskere som Jens Christian Skou.

I december offentliggjorde et internationalt ekspertpanel sin evaluering af den nye universitetslov fra 2003 og fusionerne i 2007, og derfor er debatten om universiteterne aktuel. Netop den sidste af de to begivenheder markerer i følge Claus Emmeche en milepæl i vilkårene for forskning i Danmark. Det år bryder politikerne med den klassiske arbejdsdeling mellem forskningens typer. Indtil da forsker industrien for sine egne penge og for at tjene flere. Sektorforskningen får sine opgaver og sine midler fra ministerierne. Kun universiteterne er fri til at forske for forskningens egen skyld, uden kassen smækkes i. For 2007 er ikke kun året, hvor Aarhus School of Business og Aarhus Universitet bliver til ét. Samtidig lægges universiteterne sammen med en række af sektorforskningens institutioner.

»Nu har de også overtaget sektorforskningsinstitutionernes udfordring. De skal sørge for, at ministerierne bliver ved med at synes, at de gider finansiere deres forskning. Det betyder, at de bruger en stor del af arbejdstiden på at retfærdiggøre sig ved at lave stadig nye kontrakter med aftagere af forskningen«, forklarer Claus Emmeche.

»Det entreprenante universitet«, kalder han en ny tid, hvor den dygtige forsker ikke kun er ham, der med møjsommelig flid skræller lag på lag af den menneskelige uvidenhed. Her bliver »vinderen den forsker, som er god til at fremstå dynamisk og god til at netværke. Det er ham, som kan brande sig selv og sin forskning, og som brænder for at være entreprenant og skrabe midler til sig«, siger lektoren.

For samfundet vil se udbyttet af indskuddet og mere år for år. Og mens

basismidlerne til den famlende grundforskning svinder med to procent, hver gang året skifter, stiger risikoen for, at konkurrencekulturens negative bivirkninger for alvor slår ud i Danmarks akademiske miljøer.

### Skattesnyd

I enheden Nanea begynder forfaldet at hænge. En dag får Anja et brev med posten. Det er fra SKAT, og der står, at SKAT har fået et anonymt tip, der blandt andet drejer sig om Anja. Hun er en blandt flere medarbejdere, der modtager offentlige midler, som hun ikke er berettiget til.

Anja er ansat i løntilskudsordning. Mere præcist får Anja løntilskud og et beløb, som Poul Thorsen lægger oven i hver måned, så hun ender på den rigtige løn for sit fuldtidsarbejde. Det er ikke lovligt. Til gengæld er det et vilkår for hendes ansættelse. Brevene giver uro. Der er flere, som skal betale mange penge tilbage. De konfronterer Poul Thorsen med det.

»Det er rigtig træls for jer«, mener chefen og stikker Anja en skrivelse, som er dateret tilbage til hendes ansættelses start. Der står, at hun får dækket udlæg til rejser og udstyr, og meningen er, at Anja giver brevet til SKAT og slipper for sin regning.

Skattesagen viser to ting. Den ene er, at økonomien halter så meget i Nanea, at flere medarbejdere lønnes ulovligt. Den anden er, at det er håbløst at tale med chefen om problemet. Poul Thorsen bliver »ulden i munden«, når han bliver krævet et svar, forklarer Toke. Alle bemærker, at der er vandtætte skotter mellem manden på gulvet og Naneas økonomi. Forskerne kan ikke få at vide, om det er millionerne fra CDC eller midler fra andre investorer, der betaler deres løn. Ingen kan få at vide, hvor pengene bliver af, og om der er nok til at gøre de enkelte projekter færdige.

Til gengæld slår chefen ikke skår af forventningerne til fremtiden.

»Man kan sige meget, men han var god til at få ideer, og der kom flere og flere«, siger Anja, som også forklarer, at retorikken lægger et omhyggeligt spin, der afleder opmærksomheden fra ulden i Poul Thorsens svar og motiverer alle til at blive ved.

Poul Thorsen fortæller sin enhed om dygtige, nye kollegaer, der kan starte i morgen, hvis bare naneanerne tager fat og hjælper med at skaffe midler hjem. Han tegner i luften og på sine plancher og fortæller om *blood spots* og andre projekter, som forskningen kan udbygges med, når strømmen vender.

»I må lægge i puljen til det fælles bedste. Så trækker vi dobbelt så meget ud næste år«, opmuntrer Poul Thorsen, og Lise konstaterer, at Nanea lever, som chefen dirigerer.

»Det gør man jo i en familie. Man strækker sig for hinanden«.

Men strømmen vender ikke i Nanea. I 2008 pakker Poul Thorsen sin kuffert og flytter til Atlanta. Toke opfatter det, som om han stikker af. Chefen for det hele efterlader forskerne i det store hus og i en økonomisk sump, som kun han er ansvarlig for. Efter nytår siger Poul Thorsen sin stilling op. Nanea dør med sin fader, mens skandalen samler sig omkring ham.

### Forført

På Frederiksberg holder Dansk Magisterforening til. Her er mange af universiteternes naturvidenskabelige forskere organiseret, og Jens Vraa-Jensen er konsulent for en del af dem. Fuskeriet på Aarhus Universitet kommer ikke bag på ham. Økonomiske krumspring som for eksempel Anjas kreative lønpakke bliver som regel stoppet af de lokale tillidsmænd på universiteterne, før DM overhovedet hører om dem. Alligevel er Jens

Vraa-Jensen stødt på 10 forespørgsler om ulovlige løntilskudsordninger de seneste år, og årsagen er klar ifølge ham. Det er »rimelig unikt« på det danske arbejdsmarked, at ansatte i universitetsverdenen skal møde på arbejde med deres egen løn i rygsækken - og at de ryger ud, hvis manøvren mislykkes. Sidste år sagde det Naturvidenskabelig Fakultet i København farvel til 70 medarbejdere på grund af nedskæringer. Fyringerne giver et vink med en vognstang om de egenskaber, der kendetegner den dygtige medarbejder ved Danmarks højere læreanstalter:

»Afskedigelserne ramte kun dem, der var på finansieret af faste bevillinger og i princippet burde have den sikreste ansættelse, mens dem på de eksterne projekter gik fri. Så begynder nogle forskere at kigge efter måder, som de kan forbedre deres økonomi på,« konstaterer Jens Vraa-Jensen.

Den analyse vækker genklang på Center for Naturfilosofi og Videnskabsstudier. Her angriber Claus Emmeche det universitetssystem, der hylder fundraiseren og entreprenøren frem for den omhyggelige fagnørd. Solen skinner på den, der én gang har bevist, at han kan rejse store midler, og som holder liv i håbets flamme om, at der vil komme mere. Han får lov at være i fred, og sådan frister det entreprenante universitet »visse Stein Bagger-typer til at begå fusk og svindel«.

Nanea er død. Men projekterne bliver gjort færdige under nye rammer, og endnu et arbejde spræller i den gamle enhed. Eks-naneanerne kæmper med at forstå, hvad der egentlig skete. For Toke er sagen klar: Han arbejdede under en enestående chef med en lige så ubegribelig moral, men chefen fik lov at strække ud i en verden, der gav plads til hans tilbøjeligheder.

»Vi har skabt et meget konkurrencebetonet system, hvor store summer går til enkeltpersoner med store forskningsgrupper under sig, og det favoriserer på en måde den slags mennesker. Hvis du kan sælge dig selv, bolttrer du dig i det her system. Hvis du ligefrem er skruppelløs og ikke skyer kriminelle handlinger, kan du i hvert fald for en tid boltre dig, så jeg tror ikke, at det er den sidste sag, vi ser«.

Poul Thorsen var den ny tids mand. Han »vil have sine armbevægelser«, og han »bandede og svovlede altid over alt bureaukratiet«, siger Lise. Men ideerne var gode, og derfor begreb hun ikke, at skuden var rådden, før den sank. Den overraskelse vil Lise gerne spare andre for.

»For mig er det en forførelseshistorie. En agitatoring. I universitetsverdenen hylder man pertentligheden i forskningen. Vi skulle gøre alting nøjagtig ens, og vi skulle opfylde de strengeste forskningsmæssige kriterier. Der går lang tid, før du tænker, at nogen spiller spillet på en helt anden måde.«

## PS

Fortællingen om Nanea bygger på samtaler med Toke, Lise og Anja om, hvad de hver især har oplevet deres tid i Nanea. Østjyllands Politi, Aarhus Universitet og Forsknings- og Innovationsstyrelsen har bidraget med baggrundsviden. Toke, Lise og Anja er opdigtede navne. Information kender deres rigtige identitet.

Information har kontaktet Poul Thorsen gennem hans danske advokat, Jan Schneider. Poul Thorsen ønskede ikke at medvirke i artiklen, men Jan Schneider fastholder, at hans klient er uskyldig.

## Naneas storhed og fald

2000 Nanea oprettes med en bevilling på 7,8 millioner dollar fra den amerikanske sundhedsinstitution Centers for Disease Control and Prevention (CDC). Bevillingen administreres af Forsknings- og



Innovationsstyrelsen under direktion af Poul Thorsen.

2007 Projektet forlænges med en ny bevilling fra CDC på 8,2 millioner dollar.

2008 Poul Thorsen flytter til Atlanta, men er fortsat videnskabelig og administrativ chef for Nanea.

Vinter 2008-2009 Aarhus Universitet opdager, at der ikke er de midler til rådighed for forskningen, som Nanea har brugt. Poul Thorsen forsikrer, at der er penge på vej fra USA og kan fremvise tilkendegivelser om bevillingerne som dokumentation.

Marts 2009 Poul Thorsen opsiger sin stilling ved Aarhus Universitet. Nanea nedlægges, men projekterne fortsætter under ny administration.

Forår 2009 Aarhus Universitet opdager, at tre skrivelser om bevillinger fra CDC øjensynligt er forfalskede, ligesom CDC heller ikke anerkender endnu en skrivelse om et udestående beløb på Naneas første bevilling. I alt omfatter de falske underskrifter et beløb på knap to millioner dollar.

Maj 2009 Forsknings- og Innovationsstyrelsen indgiver en politianmeldelse. Anmeldelsen retter sig ikke mod nogen navngiven person.

Efterår 2009 Aarhus Universitet opdager, at Poul Thorsen har opretholdt en dobbeltansættelse som lektor i Danmark og professor på Emory University i Atlanta, som Aarhus Universitet ikke har godkendt.

Januar 2010 Aarhus Universitets direktør Jørgen Jørgensen undsiger Poul Thorsen i en meddelelse til Nanea-projekternes samarbejdspartnere. Meddelelsen nævner også bedrageri-sagen.

Februar 2010 Århus Stiftstidende tager sagen op og landets øvrige medier følger efter.

Marts 2010 Østjyllands Politi efterforsker fortsat med henblik på at rejse en sigtelse mod sagens nøgleperson.

#### PS

Fortællingen om Nanea bygger på samtaler med Toke, Lise og Anja om, hvad de hver især har oplevet deres tid i Nanea. Østjyllands Politi, Aarhus Universitet og Forsknings- og Innovationsstyrelsen har bidraget med baggrundsviden. Toke, Lise og Anja er opdigtede navne. Information kender deres rigtige identitet.

Information har kontakten Poul Thorsen gennem hans danske advokat, Jan Schneider. Poul Thorsen ønskede ikke at medvirke i artiklen, men Jan Schneider fastholder, at hans klient er uskyldig.

#### Naneas storhed og fald

2000: Nanea oprettes med en bevilling på 7,8 millioner dollar fra den amerikanske sundhedsinstitution Centers for Disease Control and Prevention (CDC). Bevillingen administreres af Forsknings- og Innovationsstyrelsen under direktion af Poul Thorsen.

2007: Projektet forlænges med en ny bevilling fra CDC på 8,2 millioner dollar.

2008: Poul Thorsen flytter til Atlanta, men er fortsat videnskabelig og administrativ chef for Nanea.

Vinter 2008-2009: Aarhus Universitet opdager, at der ikke er de midler til rådighed for forskningen, som Nanea har brugt. Poul Thorsen forsikrer, at der er penge på vej fra USA og kan fremvise tilkendegivelser om bevillingerne

som dokumentation.

Marts 2009: Poul Thorsen opsiger sin stilling ved Aarhus Universitet. Nanea nedlægges, men projekterne fortsætter under ny administration.

Forår 2009: Aarhus Universitet opdager, at tre skrivelser om bevillinger fra CDC øjensynligt er forfalskede, ligesom CDC heller ikke anerkender endnu en skrivelse om et udestående beløb på Naneas første bevilling. I alt omfatter de falske underskrifter et beløb på knap to millioner dollar.

Maj 2009: Forsknings- og Innovationsstyrelsen indgiver en politianmeldelse. Anmeldelsen retter sig ikke mod nogen navngiven person.

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#### Denne artikel er anbefalet af:



Troels Hansen

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## Kommentarer

Man skal være registreret bruger for at skrive kommentarer på information.dk. Som registreret bruger får du også mulighed for at tilmelde dig nyhedsbreve m.m. [Tilmeld dig her](#)

[God tone i debatten](#)



**Ole Gerstrøm siger:**

Berlingske skrev, at enhedens forskningsmæssige resultater ikke er anfægtet. Denne konklusion forekommer at være forhastet. Fra kriminologien ved vi, at den typiske bedrager bliver hooked. Det skal blive ved, og blive ved.

Forskningsenheden Nanea havde bl.a. "dokumenteret" mangel på sammenhæng mellem kviksølv vacciner og autisme.

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## Læs også



### **Bombningen af Den Franske Skole blev redigeret ud af erindringer**

En af Danmarkshistoriens største tragedier blev bevidst udeladt, da besættelsestidens historie skulle formidles på film - og det skete efter pres fra ministerielt niveau, afslører historiker. Filmen 'De Fem Aar' har formet generationer af folkeskoleelevers forståelse af Anden Verdenskrig. Den katastrofale fejlbombning af Den Franske Skole er ikke nævnt med ét ord



### **Er finanskrisen for kompliceret til retssystemet?**

En sag om svindel med derivater for 500 mio. euro, der nu undersøges af Island, blev i første omgang afvist af de engelske finansmyndigheder. Årsag: De finansielle redskaber var for komplicerede til, at en jury ville fatte dem



### **Danske læger blev brugt i asbest-coverup**

Ved en dansk overlæges mellemkomst blev arbejdere i en FLSmidt-kontrolleret mine på Cypern erklæret raske, selv om de i årevis var udsat for livsfarligt asbeststøv. Selv var overlægen bestyrelsesmedlem i FLSmidt og svigersøn til hovedaktionæren i den danske industrigigant



### **Kan de ældre biografgængere redde filmbranchen?**

En stille revolution er i gang: Seniorer strømmer i biografene, men det er ikke 'special effects', der lokker det modne publikum: De higer efter at se store karakterskuespillere, voksne dramaer og fortællinger om sent blomstrende kærlighed, og nu sadler filmbranchen om for at imødekomme fremtidens målgruppe



### **Derfor er Bitterfissen blevet så interessant**

I søndags løftede en af Danmarks mest populære bloggere sløret for, hvem der gemte sig bag pseudonymet Bitterfissen Bethany. Information løfter nu

sløret for, hvad der ligger bag hendes succes i blogosfæren



### Danmark udleverer fanger til afghansk tortur-fængsel

Afghanistans største menneskeretsorganisatie AIHRC, rapporterer om flere tilfælde af tortur i det fængsel, Danmark udleverer fanger til. Forsvarsminister Nick Hækkerup (S) løber fra sit løfte om at suspendere fangeudleveringen. Danmark overtræder sine konventionsforpligtelser, mener både Amnesty International og AIHRC

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## Mest læste

Thorning laver finanslov med Enhedslisten

Bombningen af Den Franske Skole blev redigeret ud af erindringen

Thorning kræver homovielser i kirkerne

Regeringen forsøger at spinne sig ud af afghansk torturproblem

Irak er ramt af bølge af terrorbomber

Rinko Kawauchi

Thorning: Tobinskat tilbage på tegnebrættet

Utøya-offer fik prins Charles til at le

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## Mest sendte

Venstre vandt værdikampen, men

tabte sig selv

Bombningen af Den  
Franske Skole blev  
redigeret ud af  
erindringen

'Det gør lige så ondt på  
mig, som det gør på dig'

I Herning bliver de  
unge på uddannelserne

Skal der slukkes for min  
velfærdsrespirator?

Psykiatrisnit i Odense  
får hård kritik

Danske læger blev  
brugt i asbest-coverup

Kan de ældre  
biografængere redde  
filmbranchen?

EXHIBIT 19

# **“Something is Rotten, But Not Just In Denmark”**

Remarks of Rep. Dave Weldon, M.D. (R-FL)  
Autism One Conference  
Chicago, Illinois

May 29, 2004

It is a pleasure to be here with you today. I am pleased to see that the Autism community is more united today than they have ever been. I have said repeatedly that the Autism Community is the 900-pound gorilla that has not had its voice heard adequately on Capitol Hill.

That is largely due to the endless demands on your time, effort, emotions, and money in caring for the unique needs of your children. There is little left to engage the public at large and the Congress in particular. I see that changing. Certainly, last week’s Institute of Medicine “report” has had one positive effect, it has united and reinvigorated you and the parents of autistic and vaccine injured children across this nation.

I want to make it clear that I support vaccinations. My 5-year-old son has had all of his vaccinations. Someone in the media last week tried to portray me as a “vaccine skeptic.” After reviewing my record on this issue and all of my statements in the past, the newspaper printed a retraction. This however, seems to be part of a pattern – to vilify those who simply ask if our vaccines could be safer.

Friends, I practice what I preach. I support vaccinations and gave them to thousands of my patients and my own son. However I also believe it is appropriate to acknowledge that, like with any medical intervention, different individuals respond differently. We are all unique, we all have a different genetic makeup, and what may cause no harm in one individual just might cause harmful in another.

Since we established the vaccine compensation program in the late 1980s several thousand individuals have been compensated for vaccine injuries. We know there are adverse reactions, and I believe it is important that we dedicate resources to better understand why some children have them.

For too long, those who run our national vaccination program have viewed those who have adverse reactions, including those with severe adverse reactions, as the cost of doing business. Furthermore, the vaccine compensation program which was designed to be a no-fault compensation system has become so adversarial that only the most obvious of cases receive compensation and too many parents feel that the program is not worth the agony.

The questions that I have raised and continue to raise about vaccines are several. The number one question has been whether neurological problems were caused in some children by the high levels of mercury contained in many vaccines in the 1990s. Mercury is a neurotoxin. And, in the



1990s children – infants and unborn children – were exposed to significant amounts of mercury at the most critical point of their development.

Is the Autism community united now in their effort to see that research into the possible association between vaccines and neurodevelopmental disabilities is investigated? You bet!

Autism One, Defeat Autism Now, Cure Autism Now, Unlocking Autism, The Autism Society of America, Unlocking Autism, Moms Against Mercury, The National Autism Association, No Mercury, and The National Alliance For Autism Research have all expressed objections to the IOM report and have united behind the need to ensure that the federal government commits the necessary research to fund the biological and clinical research needed to get at the facts.

Just what is so wrong with the IOM report? What has caused all of the Autism groups to unite against the IOM?

In my 10 years of service in the US Congress, I have never seen a report so badly miss the mark. I have heard some weak arguments around Washington and I can tell you that those in the IOM's recent report are very weak. Examine this report in detail. It is plagued with serious flaws.

On January 15 of this year I wrote Dr. Julie Gerberding, the Director of the CDC, I asked her to post-pone the February 9, IOM meeting and this report because of my concern that this was not an exercise in discovering the truth but was instead a meeting “being driven by a desire to short-circuit important research and draw premature conclusions. If the purpose of this meeting is to seriously consider and address these concerns” I wrote, “then this will not be accomplished.”

Allow me to quote further from my letter to Dr Gerberding:

“It appears to me not only as a Member of Congress but also as a physician that some officials within the CDC's NIP may be more interested in a public relations campaign than getting to the truth about thimerosal.”

“Pressing forward with this meeting at this time, I believe, will further undermine the credibility of the Centers for Disease Control (CDC) on matters of vaccine safety and do damage to the reputation of the IOM. I believe the proposed date of this meeting, which you have the ability to change, is in the best interests of no one who is seeking the truth about a possible association between vaccines and neurodevelopmental disorders, including autism.

In a follow-up telephone conversation to me on February 3, 2004, Dr. Gerberding assured me that the IOM's February meeting was “not an attempted draw conclusions” but merely to “update on the science” of where we are at this point in time. However, it clearly draws conclusions and in what is perhaps the greatest outrage it goes further to call for a halt to all further research.

A public relations campaign, rather than sound science, seems to be the M.O. of the officials at the CDC's National Immunization Program (NIP) office. Why do I say this? Let's look, not only at the timing of the IOM meeting in February, the content of the IOM report, but also at studies the IOM used as a basis for their decisions. The IOM bases their decision almost entirely on five

epidemiology studies, all of which were conducted by researchers with an interest in not finding an association, all of which have shortcomings, and all of which the IOM declares would miss an association if it were in a genetically susceptible subset of children.

Not only the timing of the IOM meeting raises suspicions, but also the narrowing of the scope of inquiry, and the emphasis IOM was to assign to epidemiology.

In 2001, the Institute of Medicine concluded that “exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders.” The IOM also recommended that children not be given mercury-containing vaccines. What was the response of the CDC? For this most recent report they narrowed the IOM’s scope to looking just at Autism. Does that sound like an agency interested in understanding whether or not thimerosal might be harmful, to some children? Or, does this response lead one to conclude that they are more interested in designing something to reassure an increasingly skeptical public?

Unlike 2001, this time the IOM was directed by CDC to only consider the possible relationship between thimerosal and Autism, rather than NDDs as a whole. Anyone familiar with the Verstraeten study knows exactly why the IOM’s scope was narrowed – because the 2003 Verstraeten study found associations between thimerosal and NDDs and some children with autism may have been misdiagnosed as having speech or language delay.

By narrowing the scope – which largely went unnoticed by the media – the CDC has avoided acknowledging that thimerosal very well may have caused NDDs in some children. This latest IOM report is simply part of a P.R. campaign in my view. Would we not have had a much more productive report if the CDC had updated the research on possible associations between thimerosal and NDDs as a whole.

In evaluating thimerosal’s relationship to Autism, the IOM relies almost exclusively on five epidemiology studies. The principal authors of all five studies have serious conflicts of interest. All five studies were published in 2003 leading up to the IOM’s February 2004 meeting. All were conducted while the CDC and NIH virtually ignored the IOM’s 2001 biological and clinical research recommendations.

It is critical to note the instructions that the IOM was given, primarily by the CDC, which has been funding the IOM. Pages 5 and 6 of the IOM report make it clear that epidemiology was to reign supreme. In the absence of epidemiological evidence to support causality, IOM was instructed to give biological evidence little consideration, and was prohibited from allowing biological evidence to lend evidence toward causality.

Is it any wonder that the CDC has spent the past two years dedicating significant funding to epidemiology while starving funding for clinical and biological research? The IOM notes in their report that the epidemiology studies they examined were not designed to pick up a genetically susceptible population. Yet, they attempt to use these five flawed and conflicted statistical studies to quash further research into the possible association between vaccines and autism. This report is extreme in its findings and recommendations. The IOM process became little more than an attempt to validate the CDC’s claims that vaccines have caused no harm,

while quashing research to better understand whether or not and how the MMR or thimerosal might contribute to the epidemic of neurodevelopmental disorders, including autism.

I would like to turn now to the specifics of these five studies.

### **Verstraeten Study – Pediatrics, November 2003**

The Verstraeten study has been the subject of considerable criticism. This study, published in November 2003 in *Pediatrics* the journal of the American Academy of Pediatrics was released with much fanfare and public relations “spin.” Much has been written exposing the study’s methodological problems, findings, and conclusions. Most importantly however, is that this study did not compare children who got thimerosal to those who did not. Instead, its CDC-employed authors focused primarily on a dose response gradient.

In addition to the study itself, it is important to note the public relations “spin” surrounding this study.

On the day the Verstraeten study was released, a top CDC researcher and a coauthor of the study was quick to declare to the news media that, “The final results of the study show no statistical association between thimerosal vaccines and harmful health outcomes in children, in particular autism and attention-deficit disorder.” Let me repeat that, “The final results of the study show no statistical association between thimerosal vaccines and harmful health outcomes in children, in particular autism and attention-deficit disorder.”

The newspaper headlines of the day read:

- “Study Clears Vaccines Containing Mercury” *Associated Press* and *USA Today*,
- “CDC Says Vaccines are Safe...” *The Seattle Times*

While that was the spin of the day, allow me to quote from the study. “... we found no **consistent significant associations** between TCVs [thimerosal containing vaccines] and neurodevelopmental outcomes. In the first phase of our study, we found an association between exposure to Hg from TCV and some of the neurodevelopmental outcomes screened. In the second phase, these associations were not replicated for the most common disorders in an independent population.” They did find associations, but as they changed the study most of the associations, but not all, disappeared.

Furthermore, in a January 2004 article this lead co-author was forced to admit that many children in the study were too young to have received an autism diagnosis. He went on to admit that the study also likely mislabeled young autistic children as having other disabilities thus masking the number of children with autism.

The message from the CDC to media was that there is nothing to be concerned about, but the study said something somewhat different. The news media too a large degree took the CDC’s spin hook, line, and sinker, and largely chose not to read the study itself.

Five months after the article was published, and largely after the IOM report had been written, the lead author of the study, Dr. Thomas Verstraeten broke his silence in a letter to *Pediatrics*

stating: “The bottom line is and has always been the same: an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and therefore, more study is required.”

Dr Verstraeten the lead author of the study says that an association between TCVs and NDDs cannot be refuted based on his study, yet the IOM in their assessment of the same study state that it is a basis for concluding that “there is no association between thimerosal-containing vaccines and autism.”

The IOM acknowledges that Verstraeten would not have picked up an association in a genetically susceptible population. The IOM also noted that the study was limited in its “ability to answer whether thimerosal in vaccines causes autism because the study tests a dose-response gradient, not exposure versus non-exposure.”

It is also critical to note that the Verstraeten study cannot be validated. The earlier datasets have been destroyed and the only datasets the CDC will make available to outside researchers are the ones that they have already manipulated. The raw, unaltered data is not available. Additionally, outside researchers are held to a much more restrictive access to information than are CDC researchers. Only one independent researcher has been granted access to the CDC’s VSD database and the CDC has kicked those researchers out based on ridiculous reasons. They claimed their research methods might infringe on privacy. Yet the database contains no names. The researchers do not even know what HMO the patient is enrolled in. Nor do they know what state the subjects live in. There is no way for an individual to be identified through their research.

### **Hviid Study**

The IOM cited the 2003 study by Hviid of the Danish Population as one the key studies upon which it bases its conclusions.

Let’s consider first the conflict of interest of the principal author. Hviid works for the Danish Epidemiology Science Center which is housed at the Staten Serum Institute (SSI) the government owned Danish vaccine manufacturer. Also, all of his coauthors either work with him at the Center or are employed by SSI. Staten Serum Institute (SSI) makes a considerable profit off the sale of vaccines and vaccine components and the U.S. is a major market for SSI. SSI has \$120 million in annual revenues and vaccines are the fastest growing business segment accounting for 80% of its profits. Both the U.S. and U.K. are important export markets for SSI’s vaccines and vaccine components.

Furthermore, if Hviid were to find an association between thimerosal and autism, SSI with which he and his Center are affiliated would face significant lawsuits. These facts are important and are critical when evaluating this study. Furthermore, this study only looked at Autism and not neurodevelopmental disorders as a whole.

Mercury exposures in the Danish population varied considerably from those in the U.S. Danish children received 75 micrograms of mercury by 9 weeks and another 50mcgs at 10 months. By

comparison, children in the U.S. received 187.5 mcgs of mercury by age 6 months – nearly 2 1/2 times as much mercury as Danish children in just the first 6 months of life.

Dr. Boyd Haley has said that comparing the exposures in the US to those in other countries is like comparing apples and cows. I think there is a lot of truth to that.

Hviid states that the rate of autism went up after they began removing thimerosal from vaccines in 1992. The numbers in Hviid study are skewed in that they added outpatient Autism diagnosis to the number after 1992. The IOM notes other limitations of the study including the differences in the dosing schedule and the relative genetic homogeneity of the Danish population.

Yet even with these serious limitations, the committee concludes that this study has a “strong internal validity,” finding an increase in autism after removal of thimerosal.

Like the Verstraten study, Hviid would not be able to pick up a group of children who were genetically susceptible to mercury toxicity.

Danish autism rate is about 6 in 10,000 vs. 30 in 10,000 in the U.S. – once again we are comparing apples and cows. Indeed, I believe it can legitimately be argued that the lower rate of Autism in Denmark is attributable to the lower exposure to mercury in their population

### **Madsen Study**

Next the IOM relies on the study by Madsen et al., once again examining virtually the same population that Hviid examined. Again, the relevance of the Danish experience to the U.S. experience is limited in that the Danish population is genetically homogenous and had significantly lower thimerosal exposures than children in the U.S.

Let’s consider the conflicts of interest with this study. First of all, two of Madsen’s coauthors are employed by the Staten Serum Institute. Additionally, like Hviid, two of Madsen’s coauthors work directly for the Staten Serum Institute (SSI) – the Danish vaccine manufacturer which exports vaccines and vaccine components to the U.S. and which faces liability if an association is found. Madsen works for the Danish Epidemiology Science Center – which is affiliated with SSI.

This study, like Hviid, added outpatient cases into the number of cases of autism after 1995. The authors acknowledged that this addition might have exaggerated the incidence of autism after the removal of thimerosal. The IOM acknowledged that this limits the study’s contribution to causality.

### **Stehr-Green Study**

The IOM relied on the Stehr-Green study which examined the Danish population (do you see a pattern yet?) and Swedish populations and attempted to compare that to the U.S. population. Furthermore, a key coauthor of this study is employed by the Danish vaccine manufacturer - Staten Serum Institute.

I will not repeat the problems with the Danish data again, but with regard to Sweden it is important to note the children there received even less thimerosal than children in Denmark – receiving only 75 mcgs by age 2. Furthermore, the authors included only inpatient autism diagnoses in the Swedish population. The IOM notes that the ecological nature of this data “limits the study’s contribution to causality.” But they site it anyway.

### **Miller et al.**

The Miller study examines the population of children in the United Kingdom. This study is still unpublished which limits a critical and public evaluation of its findings.

Dr. Miller has actively campaigned against those who have raised questions about vaccine safety. She and her department receive funding from vaccine manufacturers, and she reportedly serves as an expert witness on behalf of vaccine manufacturers who are being sued.

This study, like the Verstraeten study is a dose response study which is limited in that it does not compare children who received thimerosal to those who did not.

Children in the U.K were exposed to up to 75 mcg of mercury by 4 months of age. This represents about one-half of what children in the US would have been exposed to by this age, plus children in the U.S. got another 50 mcg two months later at age 6 months for a total exposure in the first six months of life of nearly 2 1/2 times what children received in the U.K.

The author concludes that the study found no association between increasing exposures to thimerosal and Autism.

### **Conclusion on Epi studies.**

You can see clearly why the IOM is on very shaky ground in drawing the conclusions they did. They based their decision on five epidemiology studies:

- Three of them examining the genetically homogenous population of Denmark.
- At least one employee of the Staten Serum Institute serves a coauthor of at least 3 of the studies.
- Only one study examining the U.S. population – and that study did not compare those with no mercury exposure to those with exposures.
- Four of them with populations receiving less than half of the mercury exposure that children in the U.S. received
- None of them with any ascertainment of prenatal or postnatal background mercury exposures.
- None of them considering prenatal exposures which may have given children
- None of them able to detect a susceptible subgroup that many have had a genetic susceptibility to mercury toxicity.
- Three of them failing to address how the addition of outpatient cases of Autism in Denmark might have perilously skewed the results.
- Four of them examined populations with autism rates considerably below that in the U.S.
- One of the studies has not been published and not subjected to public review.

## **Bio/Clinical Research - Thimerosal**

Since the release of the IOM's report in 2001, public health officials in the US virtually ignored the biological and clinical research recommendations. While the CDC had no trouble funding epidemiology studies – all with their flaws and inadequacies – several critical biological and clinical research recommendations were starved of funding:

The IOM recommended that the following studies be done, but the CDC and the NIH failed to dedicate the resources to fund these studies:

- Identify primary sources and levels of prenatal and postnatal background exposures to thimerosal, including Rho (D) Immune Globulin in pregnant women and other forms of mercury (fish) in infants, children and pregnant women – NOT DONE;
- Compare the incidence and prevalence of NDDs before and after removal of thimerosal from vaccines. NOT DONE and the CDC tells me they will not begin such studies until 2006.
- Research how children, including those with NDDs, metabolize and excrete metals – particularly mercury- NOT DONE
- Conduct research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposures from other sources – NOT DONE
- Conduct careful, rigorous and scientific investigations of chelation when used in children with NDDs, especially Autism. NOT DONE though in their latest report they urge that this be highly restricted.
- Conduct comparative animal studies of the toxicity of ethylmercury and methylmercury to better understand the NDD effects of thimerosal – ONLY PARTIALLY DONE – but with very little federal support.

In 2001 the IOM stated that it is “unclear whether ethylmercury [from vaccines] passes readily through the blood-brain barrier...” The IOM recommended several biological and clinical studies to answer this question and whether this mercury could cause developmental problems. These studies were in large part never done. Yet IOM chose to ignore the need for this research and instead has focused its analysis on the data available today, most of which is statistical data.

There is much more research that needs to be done before it can definitively be said that thimerosal does not contribute to NDDs. Even today, the IOM cannot tell you with any degree of certainty what happens to ethylmercury once injected into an infant. Does it go to the brain? Does it cause developmental problems? Who knows?

## **MMR – Autism Association**

Allow me to touch briefly on the IOM's analysis of the MMR-Autism issue. They devoted only one hour of discussion to this topic at the February meeting and failed to invite those who were most intimately involved in this research to present to the IOM.

As with thimerosal, the IOM relied almost exclusively on epidemiology. They made their decision about whether or not measles may be related to Autism in children, by reviewing 13 statistical studies in which many of the authors have conflicts of interest. Some of these authors have been openly hostile in their assessments, which calls into question their objectivity. Also, remember it is epidemiology that reigns supreme in this review – even if the studies are flawed in their design.

The IOM still cannot answer the question as to why measles is in the intestines of some Autistic children. Why is it there? What is it doing? How did it get there? Is it contributing to Autism? The IOM attempts to explain this issue away by saying it's likely that the presence of measles could just be a co morbidity to Autism. This cavalier attitude of the IOM, the CDC, and others in the public health community is unacceptable. We have a moral obligation to fully support research to understand why vaccine strain measles is in the intestines and CSF of these children. The government mandated vaccination, the least we should do is fund research to understand why measles is persisting in these children, what harm it might be causing, and how we might best treat these children.

The NIH is only now attempting to duplicate the work of Dr. Andrew Wakefield. Despite being vilified for the last 6 years half of Dr. Wakefield's work has been demonstrated to be correct. Practitioners across the U.S. and in many other parts of the world are finding the same inflammatory bowel disease he first described in Lancet in 1998. Drawing "conclusions" at this time is counterproductive. Statistical studies are of little benefit, only a clinical pathological study will lay this issue to rest.

### **A Few Final Remarks Regarding The IOM Report**

For the reasons outlined above and other reasons, this report is premature, perilously reliant on epidemiology, based on preliminary incomplete information, and I believe may be ultimately repudiated – perhaps in short order.

This report will not deter me nor the Autism community from our commitment to seeing that thimerosal and MMR research is properly done.

This report will do nothing to put to rest the concerns of parents who believe their children were harmed by mercury-containing vaccines or the MMR vaccine.

While this report will lead many clinicians to believe that thimerosal is safe and there is no problem with the MMR, it may contribute further to an erosion in the doctor-patient relationship.

This report has dragged the IOM under the cloud of controversy that has currently engulfed CDC.

Much like the infamous 1989 study by The National Institute of Child and Human Development (NICHD) which missed the link between folic acid deficiencies and neural tube defects like spina bifida, the epidemiology studies reviewed by the IOM in drawing these findings, could easily have missed associations in susceptible populations



Finally, let's remember that the IOM is not immune to error and has been forced to reverse itself before. Most recently the IOM reversed a long-standing finding that chronic lymphocytic leukemia (CLL) was not due to Agent Orange exposures. A similar reversal is a very real possibility here.

### **H.R. 4169 – The Mercury Free Vaccines Act of 2004**

On April 2, I introduced along with Rep. Carolyn Maloney, H.R. 4169 – The Mercury Free Vaccines Act of 2004. We currently have 15 cosponsors from across the political spectrum.

H.R. 4169 will phase-out the use of mercury in vaccines over the next 3 years, giving particular attention to completely eliminating mercury from childhood vaccines on an expedited schedule.

This bill is in response to the fact that:

- The safety of thimerosal in vaccines is not proven
- Mercury is well-established as a neurotoxin.
- According to the EPA 1 in 6 newborns is born with a blood mercury level considered unsafe.
- The FDA and the EPA recently warned pregnant women, nursing mothers, and young children to limit their consumption of certain fish that are high in mercury.
- No one at the NIH or CDC can tell you what happens to the mercury once injected into an infant – Where does it go? How much goes to critical organs? How much to the brain? Can it cause damage to the developing central nervous system? No one can answer these question and they should before infants are exposed to more mercury.
- The CDC is has adopted a policy reintroducing mercury into childhood vaccines by recommending the flu vaccine for infants at 6, 7, and 23 months of age – most of which contain mercury.

If we are going to move this legislation forward, I am going to need each and everyone of you to go back and get your member of Congress to cosponsor this bill. You need to call them and ask them to cosponsor H.R. 4169. And be persistent, but not rude.

### **New Legislation to Monitor Adverse Reactions to Vaccines**

It is critical that we make improvements in how we monitor for and respond to adverse reactions to vaccines. Today there are three government agencies that have responsibilities related to monitoring the safety of vaccines – the FDA, the CDC, and the NIH.

The Food and Drug Administration (FDA) has a responsibility to monitor vaccine safety. However, their role is largely limited to ensuring that vaccine lots that are released meet FDA standards and collecting information to be entered into the Vaccine Adverse Events Reporting System (VAERS).

The NIH does not have a concerted effort to fund vaccine safety research. They provide funding for research in a haphazard manner - if you happen to submit a proposal and it passes peer

review they may fund it. The NIH has funded only a handful of studies over the past two years investigating vaccine safety issues.

The CDC has the greatest responsibility in this area. Unfortunately, they also have the greatest conflict of interest. The CDC's vaccine safety program amounts to about \$30 Million a year, and half of this goes to pay HMOs for access to the Vaccine Safety Database.

The biggest conflict within the CDC is that they are also responsible for a running \$1 Billion vaccine promotion program. The CDC largely measures its success by how high vaccination rates are. Here lies the largest conflict. Any study raising concerns that there might be adverse reactions is likely to result in safety concerns leading to lower vaccination rates. Lower vaccination rates are in direct conflict with the CDC's top measurement of success. Clearly, due to its overwhelming size and the manner in which the agency measures its success, the vaccine promotion program overshadows and influences the CDC's vaccine safety program.

In fact, rightly or wrongly, the vaccine safety office within the CDC is largely viewed by outside observers as nothing more than another arm of the vaccine promotion program, giving support to vaccine promotion policies and doing very little to investigate and better understand acute and chronic adverse reactions.

Further complicating the CDC's role and undermining their research is the fact that the vaccine safety studies produced by the CDC are impossible to reproduce. External researchers are not granted the same level of access to the raw datasets that the CDC's internal researchers are granted. The bottom line is that the CDC's studies related to vaccine safety cannot be validated by external researchers – a critical component in demonstrating the validity of scientific findings.

The CDC recently announced that a Blue Ribbon Panel will meet to examine how the CDC might better review vaccine safety. I do not hold out much hope for this panel, however, because the panel is limited in their scope. Much like the IOM was limited in the outcome they were allowed to draw, this panel is limited to deciding where within CDC, vaccine safety monitoring should be housed. The NIH recently recognized the importance of moving patient safety monitoring outside of NIH – I believe the same should be done with vaccine monitoring. It should be completely removed from the CDC's jurisdiction. The CDC is too conflicted to oversee this function.

In order to ensure that there is a concerted and independent effort within the federal government to monitor for adverse reactions to vaccines, I have prepared legislation which I will soon introduce that will ensure that vaccine safety monitoring is completely independent. It has become clear to me that the federal government has failed miserably and has not given this issue the attention that is needed. Clearly, greater oversight and complete independence is needed.

My legislation will ensure that those responsible for vaccine safety research are free from all conflicts of interest and have as their sole focus the following:

- Determining what these adverse reactions are
- Understanding why some individuals have adverse reactions, and
- How we might best ensure that such reactions are avoided.

## **Brighton Collaboration**

Finally, I want to turn my attention to something known as the Brighton Collaboration.

I am very concerned about the development of the Brighton Collaboration which began in 2000. This is an international group comprised of public health officials from the CDC, Europe, and world health agencies like WHO, and vaccine manufacturers.

This first task of the Brighton Collaborations, created several years ago, is to define what constitutes and adverse reaction to a vaccine. They have established committees to work on various adverse reactions to vaccines. Particularly troubling is the fact that serving on the panels defining what constitutes an adverse reaction to a vaccine, are vaccine manufacturers. What is even worse is the fact that some of these committees are chaired by vaccine manufacturers. It is totally inappropriate for a manufacturer of vaccines to be put in the position of determining what is and is not an adverse reaction to their product.

Do we allow GM, Ford and Chrysler to define the safety of their automobiles?

Do we let airlines set the safety standards for their airlines and determine the cause of an airline accident?

Do we allow food processors to determine whether or not their food is contaminated or caused harm?

Then, why I ask, are we allowing vaccine manufactures to define what constitutes an adverse reaction to a vaccine?

This collaboration is fraught with pitfalls and merges regulators and the regulated into an indistinguishable group.

It is critical that the American public look at what is going on here and how this entity may further erode their ability to fully understand the true relationships between various vaccines and adverse reactions.

I plan to devote additional attention to this effort.

## **Concluding Remarks**

Finally, Autism is a difficult challenge facing our nation. We have made considerable progress through groups like Autism One and the other autism organizations represented here. The work you are doing is work that must continue. I commend each of you.

I commend the researchers who are engaged to develop a deeper understanding of what is going on with these children and how we might improve their treatments. I am hopeful that the folks down at the NIH, the CDC, and the IOM will be more supportive of your work. I will do all that

I can see that critical research in all areas of autism research continue to receive increased funding.

I commend the parents who have failed to give up on their children. I commend you for your dedication to want the best for your children and for the sacrifices you have made for them.

I urge each of you to take your story to your Member of Congress and your Senator. Share your struggles with them. If I, along with the few others who have made defeating autism a top priority are to be successful, it is critical that every Member of Congress know what Autism is and that they have constituents who are watching them and asking for their help.

I urge you to tell your local television reporters and newspaper reporters your story and your struggles. Tell everyone who are willing to listen. It is through your testimony that others will know of this devastating epidemic plaguing our children.

I also urge you to share with others what is working in the treatment of your children. You are blessed with the resources that are available to you at this conference. Listen and learn from the providers here who have a lot to offer.

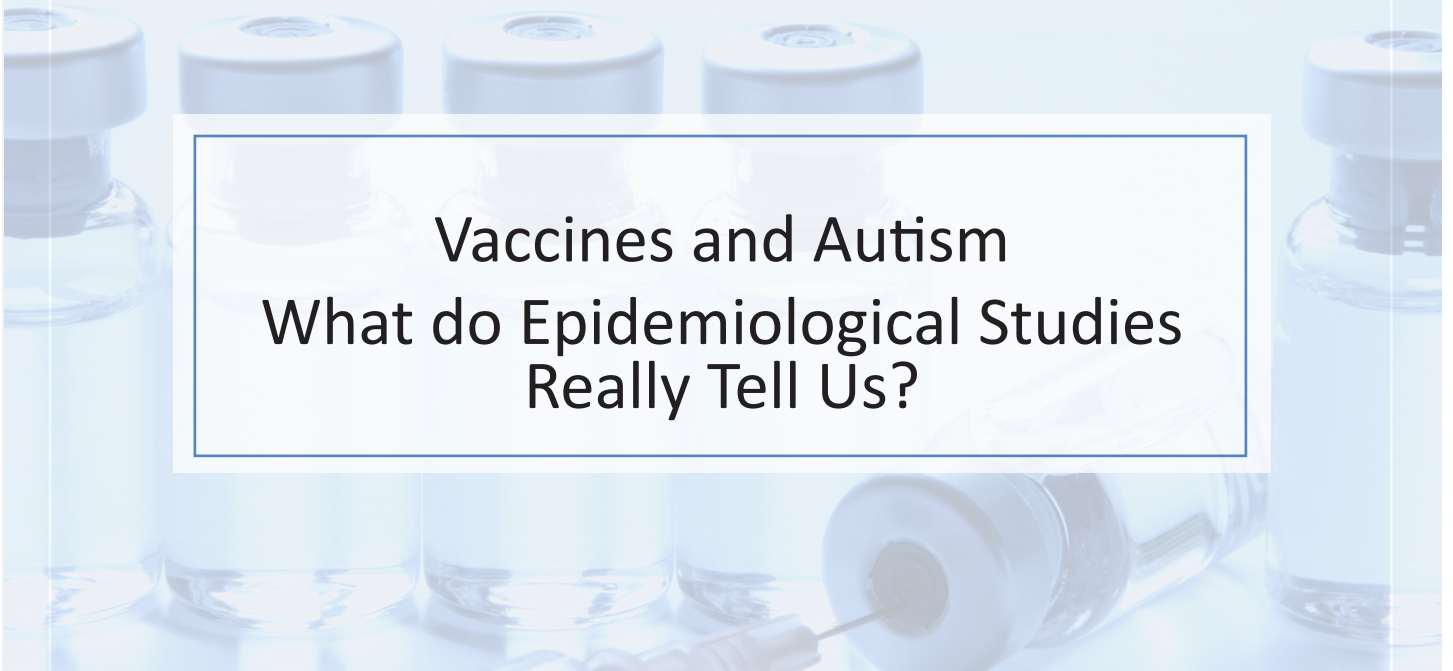
Finally, let me know what I can do to help. I stand in partnership with each of you.

Thank you for inviting me to join you today. It has been a great honor.

###

EXHIBIT 20

Vaccines and Autism  
What do Epidemiological Studies  
Really Tell Us?



# VACCINES AND AUTISM – WHAT DO EPIDEMIOLOGICAL STUDIES REALLY TELL US?

## Coalition for SAFE MINDS

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*“We have 16 studies already that clearly state that vaccines do not cause autism.”*

**-- Amy Pisani, Executive Director, Every Child By Two**

*“16 studies have shown no causal association between vaccines and autism, and these studies carry weight in the scientific industry.”*

**-- Dr. Nancy Snyderman, NBC Today Show Medical Editor**

*“The science is largely complete. Ten epidemiological studies have shown MMR vaccine doesn't cause autism; six have shown thimerosal doesn't cause autism.”*

**-- Dr. Paul Offit, “Autism’s False Prophets”**

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*“My daughter, who had been completely normal until getting nine vaccines in one day, was suddenly no longer there.”*

**--Terri Poling, RN, JD, mother of Hannah, who received federal compensation for her vaccine-induced autism.**

*“So if a child was immunized, got a fever, had other complications from the vaccines. And if you're predisposed with the mitochondrial disorder, it can certainly set off some damage. Some of the symptoms can be symptoms that have characteristics of autism.”*

**--Julie Gerberding, MD, Former Director of the CDC**

*“I think the government, or certain public health officials within the government, have been too quick to dismiss the concerns of these families, without studying the population that got sick.”*

**-- Dr Bernadine Healey, Former Director of the National Institutes of Health**

## **A NOTE FROM SAFE MINDS:**

There are 16 epidemiological studies here on MMR vaccines, thimerosal and autism. These studies represent the most often cited papers by scientists, public health officials and members of the media when trying to refute any evidence of an association between vaccinations and autism.

There are serious methodological limitations, design flaws, conflicts of interest or other problems related to each of these 16 studies. These flaws have been pointed out by government officials, other researchers, medical review panels and even the authors of the studies themselves. Taken together, the limitations of these studies make it impossible to conclude that thimerosal and MMR vaccines are not associated with autism.

In addition, Poul Thorsen, a prominent researcher responsible for a series of epidemiological studies which utilized the Danish Psychiatric Central Research Register reviewed in this report was indicted April 13<sup>th</sup>, 2011 by a federal grand jury on 13 counts of fraud and 9 counts of money laundering based on a scheme to steal grant money the CDC had awarded to governmental agencies in Denmark for autism research. According to United States Attorney Sally Quillian Yates, “Grant money for disease research is a precious commodity. When grant funds are stolen, we lose not only the money, but also the opportunity to better understand and cure debilitating diseases. This defendant is alleged to have orchestrated a scheme to steal over \$1 million in CDC grant money earmarked for autism research. We will now seek the defendant’s extradition for him to face federal charges in the United States.”

As fraud charges regarding Thorsen surface, along with our findings outlined in this report that the Denmark Register was unreliable, SafeMinds is calling for an independent federal investigation of these studies for data manipulation and scientific misconduct. Further background information on these studies, the charges against Dr. Thorsen, and documents obtained through the Freedom of Information Act that support SafeMinds’ concerns are available on our website, [www.safeminds.org](http://www.safeminds.org).

Safe Minds would like to acknowledge the previous work in this regard gathered by the “Fourteen Studies” project at Generation Rescue: <http://www.14studies.org/about.html>

One additional study on autism and thimerosal was published in September 2011 while this paper was in completed draft form. This study’s methods produced a result that demonstrated that thimerosal exposure was protective against autism. Further analysis of this study is forthcoming but not included here.



# PART 1

## MAJOR GAPS IN KNOWLEDGE

Conventional wisdom holds that the autism-vaccine question has been “asked and answered,” and that at least 16 large, epidemiological studies have thoroughly addressed and debunked any hypothesis that childhood vaccination is associated with an increased risk of autism spectrum disorder.

But there are numerous critical flaws in such an oversimplified generalization, and they are rarely given close examination by public health experts or members of the media.

It is particularly discouraging that members of the scientific community are so willing to dismiss a hypothesis that has yet to be fully tested. Overconfident pronouncements such as those found in the quotes above do nothing to advance either the cause of science or our understanding of the complex issues involved. They are, instead, the product of misunderstanding and wishful thinking, brought about by the overzealous drive to ‘disprove’ an unpopular and possibly disquieting theory.

Respected medical opinion-makers such as Dr. Snyderman and Dr. Offit mislead the public when they categorically state that there is “*no link*” between vaccines and autism. Their misguided conclusions are based on incomplete knowledge and misinterpretations, and likely to be influenced by personal and professional conflicts of interest; conflicts illustrated by their intimate and lucrative financial bonds with GlaxoSmithKline (Snyderman) and Merck (Offit), - two of the world’s leading vaccine manufacturers.

There is a host of reasons why the cavalier dismissal, by scientists and physicians, of any possible vaccine-autism association is premature, shortsighted, and wrong.

But first, some clarification about terminology. Frequently, a counter-claim to those made by the likes of Snyderman and Offit is that ‘*epidemiological*’ studies cannot be used to establish or refute, causality.

Epidemiology is the study of the distribution and determinants of disease in the human population; the basic science and fundamental practice of public health (Nordness, 2006).

Epidemiological studies may be descriptive or analytical (see for example Hennekens and Buring, 1987), Descriptive epidemiology aims to describe the general characteristics of disease distribution in relation to person, place and time. Studies of this type provide information to health care providers and those responsible for resource allocation and may also be used to generate hypotheses about disease causality, but their design precludes them from being used to test hypotheses.

The studies cited in support of ‘no vaccine-autism association’ are not flawed because they are *epidemiological*, they are, almost invariably, flawed because their aims, design, analytic procedures or conclusions have been inappropriate, and in some instances, plain wrong.

Analytical epidemiology involves using comparative studies to test hypotheses about associations between an exposure and a disease. Analytical studies can be observational or experimental, but both involve evaluation of associations between exposure and diseases, and both are well placed to do just that.

The studies frequently referred to as indicating ‘*no association between vaccines and autism*’ have, for the most part, been population-based, observational studies. As such it is quite possible for them to have helped confirm or refute the role of vaccines in causality. The reason they have failed is not because epidemiology is a ‘*blunt tool*’, nor is it because ‘*epidemiology could never pick up on such a small effect*’. It is because the studies have either been badly designed, or not designed with the right hypothesis in mind.

In the following analysis, we review and critique the analytical epidemiology studies most commonly cited as evidence against the “autism-vaccine” hypothesis. We must make clear at the outset, however, that this critique addresses only a fraction of the “autism-vaccine” connection. In fact, the studies reviewed here have explored only two discrete (and frequently confused) exposures: one vaccine, the measles-mumps-rubella vaccine (MMR) and one vaccine ingredient, the ethyl mercury based preservative, thimerosal. None of these studies have addressed possible interactions between the two exposures or the effect of these exposures in the larger context of an expanded childhood immunization program. No study has yet been conducted comparing total health outcomes in vaccinated human children with unvaccinated children. As a result, the gap between the study sample reviewed here and a full examination of vaccination exposure and autism risk remains quite large and largely unexamined.

However, with respect to the body of analytical epidemiology on MMR and thimerosal, we draw the following conclusion. The evidence in the studies that are most often claimed to provide conclusive proof dismissing a connection between these exposure and autism do not stand up to close scrutiny. Many of them do not provide evidence one way or another with respect to the hypothesis; some of them provide evidence actually supporting an exposure effect; others are too poorly designed to extract any reasonable conclusions; and in some instance the data have been manipulated in ways that border on misconduct.

In short, although the question of the connection between autism and vaccines has been asked, we have yet to see any reliable and informative answers.

## PART 2

### FLAWS AND LIMITATIONS OF MMR STUDIES

**Major Reviews** – There have been at least two major reviews of the main studies claiming to examine a potential association between MMR vaccine and autism spectrum disorders. They are the 2005 Cochrane Review and the 2004 Institute of Medicine Immunization Safety Committee Report.

#### **1) The Cochrane Review: “Vaccines for measles, mumps and rubella in children.” October 2005.<sup>1</sup>**

According to their sponsors, the Cochrane Reviews report on published (and sometimes unpublished) studies which investigate the effects of interventions for prevention, treatment and rehabilitation in a healthcare setting. Most Cochrane Reviews focus on randomized controlled trials, but other types of evidence may also be taken into account. The reviews are considered by most experts to provide the gold standard of evidence-based medical science.

In 2005, Cochrane published a review of published studies on the safety and efficacy of MMR vaccine. Their search revealed more than 5,000 papers on the subject, though only 139 of them “possibly satisfied” the reviewers’ inclusion criteria. In the end, they reported on and summarized about 31 studies, only a few of which pertained to autism spectrum disorders (ASD).

**Main results** - MMR was “likely to be associated” with febrile convulsions within two weeks of vaccination, but “unlikely to be associated” with Crohn's disease, ulcerative colitis, mumps or autism.

**General Limitations:** the authors concluded that:

- There was a moderate-to-high probability of bias in all but one of the cohort studies.
- The internal validity of some studies was problematic, and the presence of selection, performance, attrition, detection and reporting biases influenced the reviewers’ confidence in these findings. The most common type of bias was selection bias.
- There was only limited evidence of MMR’s safety compared to single component vaccines from studies with a low risk of bias. The few studies least likely to be affected by systematic error pointed to a likely association with increased febrile convulsions in the first two weeks post-vaccination.

■ The cohort studies' conclusions "that MMR is 'safe,' 'equally safe,' 'well-tolerated,' or has 'low-reactogenicity,' need to be interpreted with caution given the potential for confounding.

■ In the cohort studies, the validity of the conclusions was affected by selective reporting in the comparative analysis, with just over half the responses from participants in some cases.

■ There was a lack of clarity in reporting and systematic bias which made it "impossible" to compare the various studies through quantitative synthesis of data.

■ There were general difficulties in ascertaining adequate numbers of unexposed children due to the high uptake of vaccines and the extent of vaccination programs. This is a methodological problem likely to be encountered in all comparative studies of established childhood vaccines.

■ There was a "lack of adequate description of exposures (vaccine content and schedules)" in all cohort studies.

■ The failure of any study to provide descriptions of all outcomes was a recurring problem.

■ Some reports offered inadequate explanations for missing data, accepting as 'adequate' explanations such as 'nonresponse to questionnaire' and 'medical records unavailable'.

■ The external validity of the studies was low. Descriptions of the study populations, response rates, vaccine content and exposure - all important indicators of generalizability - "were poorly and inconsistently reported."

■ There were inadequate and inconsistent descriptions of reported outcomes, limited observation periods (maximum 42 days) and selective reporting of results. All of these problems contributed to the reviewers' decision not to attempt pooling data by study design

**SUMMARY** – Although the reviewers determined that MMR vaccine was "unlikely to be associated" with autism, they concluded that "meaningful inferences from individual studies lacking a non-exposed control group are difficult to make." They added that there were disappointed by their inability to identify effectiveness studies with population or clinical outcomes.

Many critics question how the authors of Cochrane's MMR Review could find an "unlikely" association with autism when - in the very same paper - they also concluded that:

- (a) the design and reporting of safety outcomes in MMR vaccine studies, are largely inadequate and

- (b) that critical design and reporting flaws need to be improved and standardized definitions of adverse events adopted.

Sallie Bernard, of SafeMinds, wrote that the Cochrane Review “gives MMR a free pass.” She said the review “Assumes that this version of vaccine is as safe as can be, and so beneficial there is no need to worry about the fact that the safety studies are inadequate. Would this happen for any other drug? Isn’t it possible, even probable, that the vaccine is effective but still has safety lapses and could be improved?”

In a review presented at the International Meeting for Autism Research (IMFAR) Carol Stott, a UK epidemiologist and Chartered Psychologist, wrote that, given the Cochrane Review’s conclusions, it is important to examine the extent to which the various clinical and population studies have been designed appropriately and with specific reference to the original hypothesis and, thus, to examine the extent to which claims of the hypothesis being refuted or supported are valid.

## **2) Institute of Medicine, “Immunization Safety Review: Vaccines and Autism.” May, 2004<sup>2</sup>**

In February 2004, the IOM’s Immunization Safety Committee held a hearing on the possible association between MMR, thimerosal and autism. The committee reviewed all published and unpublished epidemiological studies on causality as well as potential biologic mechanisms to explain a possible vaccine-autism causal association. Its findings were released in a May, 2004 report. The committee’s conclusions hold wide sway over many scientists, physicians and much of the media to this day.

**Main Results:** The committee concluded that the body of epidemiological evidence “favor” rejection of a causal relationship between the MMR vaccine and autism,” further stating that studies examining the association between MMR and autism consistently showed evidence of no association between the MMR vaccine and autism.

### **Limitations:**

- Because the “vast majority” of ASD cases cannot be accurately sub-classified, if there is a subset of individuals with autism syndrome triggered by exposure to vaccines, our ability to find it is very limited in the absence of a biological marker.
- Although there is no convincing evidence to date that a clearly defined subgroup with susceptibility to MMR-induced autism has been identified, genomics and proteomics could reveal in the future whether or not any genetic susceptibility to vaccine-induced autism exists.
- A lack of unexposed children is another limitation. The committee noted that they had previously called for studies to enroll children whose families opted against the MMR vaccine, but so far, this type of study has been difficult to do with sufficiently large numbers.

- The committee also noted that its 2001 report did not exclude the possibility that MMR “could contribute to autism in a small number of children because the epidemiological studies lacked sufficient precision to assess rare occurrences.”

- They also noted that it was possible that epidemiological studies would not detect a relationship between autism and MMR vaccination in a subset of the population with a genetic predisposition to autism.

The latter two points are covered in the introduction to this document. While the points are well received, it is important to note that ‘epidemiological’ studies lack neither precision nor accuracy simply by virtue of them being ‘epidemiological’. It is entirely possible to design population based studies to maximize the likelihood of identifying small effect sizes; the fact that this hasn’t yet been achieved in the vaccine-autism debate is the fault of the workmen, not the tools.

**SUMMARY:** The IOM Committee gave far more emphasis to epidemiological (population based) studies than biological studies, such as clinical studies in children, laboratory studies, and animal model studies. Since the IOM report was released in May, 2004, a large amount of biological data have been generated from several published studies to support an association between vaccines – including MMR - and ASD. A new IOM review that includes these studies is needed.

## INDIVIDUAL MMR STUDIES

The Cochrane Review and the 2004 IOM Report both referenced a number of MMR-autism studies when concluding that the evidence favors rejection of a causal association. These papers make up the bulk of the MMR investigations included in the “16 studies” referred to by Doctors Snyderman and Offit. They include nine studies on MMR:

### **1) A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism.**<sup>3</sup>

**Authors:** Kreesten Meldgaard Madsen, M.D., Anders Hviid, et. al.

**Publication & Date:** *New England Journal of Medicine*, November 7, 2002.

**Online at:** <http://content.nejm.org/cgi/content/full/347/19/1477>

**Details:** This paper is often referred to as the “Danish MMR Study”. The authors conducted a retrospective cohort study of all children born in Denmark from January 1991 through December 1998. Information on MMR-vaccination status and on autism status was obtained via Danish health records. Out of 537,303 children in the cohort, 440,655 (82.0 percent) had received the MMR vaccine. A total of 316 children with a diagnosis of autistic disorder and 422 with a diagnosis of other autism-spectrum disorders were identified (a proportion of 13.7-per-10,000, or about 1-in-730).

**Results:** After adjusting for potential confounders, the relative risk of autistic disorder among MMR-vaccinated children vs. the unvaccinated group was 0.92 and the relative risk of another autistic-spectrum disorder was 0.83. In other words, MMR-exposed children were 17-percent LESS likely to have an ASD than unexposed children: The vaccine reportedly had a statistically significant “protective effect.”

**Authors’ Conclusions:** “This study provides strong evidence against the hypothesis that MMR vaccination causes autism.”

### WHAT CRITICS SAID:

**Walter Spitzer, Professor Emeritus of Epidemiology, McGill University** et al., in a letter published in the March, 2003 issue of the *NEJM*, noted that there were still some methodological problems outstanding with regard to the Danish study.<sup>4</sup>

Spitzer charged that researchers did a clinical record review of just 40 cases (13%), which he claimed was inadequate, especially if the purpose was only to validate an existing diagnosis. Spitzer claimed that ‘...without a multidisciplinary review of original

lifetime records as well as double verification in a large descriptive single cohort, important errors would have been unavoidable, both in classification and numbers for the numerators.” Spitzer et al. also raised the question of whether pediatric clinical psychologists, pediatric neurologists and speech therapists were involved in the review and whether the reviewers were blind as to exposure status.

Though the power of the published study was high, it was “misleading,” Spitzer et al. claimed. In elaborating this point Spitzer et al. explained that if, for example, one assumed a vulnerability to MMR-induced disease in 10% of the regressive ASD cases, with 95% of this group being vaccinated, and if 80% of the non-regressive ASD cases were also assumed to be vaccinated, then “the odds ratio for MMR as a risk factor for regressive autism would be 4.17.”

However, if children with autism, regardless of sub-types, were combined and compared against non-affected controls, the odds ratio would plummet to just 0.97. “Thus a small non-statistically significant reduction in uptake of MMR in the 90% of non-regressive autistic children would mask a strong causal association in a small subgroup,” Spitzer et al. Whilst the sub-group might be small, they claim, ‘...conservatively the 10% would represent 50,000 children in the U.S. alone with a financial burden of disease to parents and government of at least \$1.25 billion per year.’”

**Goldman and Yazbak**, in a letter published in the *Journal of American Physicians and Surgeons*, pointed out the “substantial under-representation of autism diagnoses and vaccination status for children born in the later study years.”<sup>5</sup> Children with ASD in Denmark are diagnosed at about 5 years old; many were simply too young to receive an ASD diagnosis by the end of the study period. This would apply to all children under the age of 36 months and, in a practical sense, to many of the 3-5 year olds. Among children born in 1997 and 1998, who made up a substantial proportion (39%) of the total years of observation time, many had yet to even receive an MMR vaccine all.

In fact, ASD prevalence among children aged 5-9 years increased from a mean of 8.38/100,000 in the pre-licensure era (1980-1986) to 71.43/100,000 in 2000, making the adjusted prevalence rate-ratio 4.7 for the post-licensure period compared with the pre-licensure period. This suggested a temporal association between the introduction of MMR vaccination in Denmark and an almost five-fold increase in autism cases.

**Mark Blaxill, SafeMinds director**, in an unpublished critique written for SafeMinds, criticized the use of person years rather than prevalence by birth group as the choice of outcome measure. He pointed out that although person-years is common incidence measure in epidemiological studies, it is an odd choice in the study of a chronic disease like autism. He argued that “there is no really good reason (and the authors offer none) to consider duration of the disorder as opposed to its presence. Autism is generally considered a lifelong disorder, so the effect is the same among two year olds as it is among eight year olds.”



Analyzing the Denmark data using case prevalence measures reveals importance problems with Madsen et al. according to Blaxill. Most notably, he points out that the most straightforward analysis of the data provided by the study authors directly contradicts their conclusion (see table below). The actual prevalence of autism in the 440,655 children who received MMR vaccinations in Denmark was 6.1 per 10,000 as compared to the rate of 4.9 per 10,000 in the 96,648 unvaccinated children. At the population level, the risk of autism was therefore 26% higher in the group vaccinated with MMR, a calculation the authors never reported. Blaxill highlighted two biases:

<b>Unadjusted Relative Risk of Autism in MMR-Vaccinated Danish Children</b>			
	Total	Vaccinated	Not vaccinated
Population	537,303	440,655	96,948
Cases			
Autistic	316	269	47
Other ASD	422	352	70
Total ASD	738	621	117
Rates per 10K			
Autistic disorder	5.88	6.11	4.86
Other ASD	7.85	7.99	7.24
Total ASD	13.74	14.09	12.11
Relative risk			
Autistic disorder			1.26
Other ASD			1.10
Total ASD			1.16

1. *Biased exposure adjustment.* Madsen et al. introduce an adjustment for the timing of diagnosis relative to the timing of MMR vaccination. The authors determined that six of the children diagnosed with autism and seven of those diagnosed with other autistic spectrum disorders had such an early onset of the symptoms that the disorder was diagnosed before the MMR vaccine was administered. They decided that this reversed sequence of events argued against a causal role for MMR in autism, so they placed these vaccinated children in the group they called "unvaccinated" even though they had clearly received MMR vaccine. In moving autistic children into the unvaccinated group, the authors increased the pool of unvaccinated children by 13% and reduced the pool of vaccinated children by 2%. This adjustment substantially reduced the relative risk of autism among the vaccinated group, from 1.26 in the table above to 1.09 at the population level.

The MMR hypothesis argues more specifically, however, that vaccination of an otherwise normal child will contribute to an *autistic regression*. To test this hypothesis, the most relevant population would exclude all cases with early onset autism, both from the vaccinated group (as the study authors chose to do) and from the unvaccinated group (which they chose not to do). The method chosen by the authors artificially raised the incidence rate in the control group. If, instead of moving early onset (but clearly vaccinated) cases into the "unvaccinated" group, the authors had removed all early onset

cases from both groups, they would have increased the relative risk of autism in the vaccinated group to 1.28, instead of reducing it to 1.09.

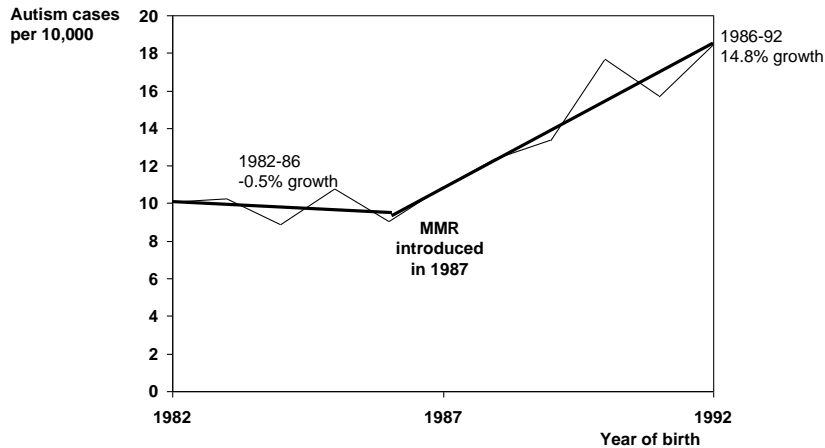
2. *Age adjustment bias effect.* The use of person-years also had a more direct effect on the published risk of MMR on autism, by introducing a skew in the sample by age group. In reporting a relative risk 0.92 (a level that suggests a protective effect of MMR in autism) rather than the case-based relative risk of 1.09, the authors weighted certain portions of their sample (the older children with more person-years) more heavily than others. Given the wide variation of risk by age, extra weight was actually given to portions of the sample with relative risks well below 0.92. Blaxill made a rough calculation of the relative risks of autism comparing children born in 1997-98 (children were one and two years of age when the data was collected) to those born between 1991-96. This calculation shows an even higher protective effect (relative risks of 0.87 and 0.77 for children with autism and autism spectrum disorders, respectively).

The distribution of relative risks is highly variable across birth years, more than would be expected under the null hypothesis of no vaccination effect. This raises questions about the quality of the vaccination data records among the older children. The apparent high rate of autism among unvaccinated older children could reflect lost vaccination records or other data integrity problems.

**Carol Stott, Mark Blaxill, and Dr. Andrew Wakefield**, claimed in the *Journal of American Physicians and Surgeons*, that Madsen et al. appeared to have adjusted inappropriately for age.<sup>6</sup> That being the case, Stott et al. argued, the findings need to be reinterpreted,” Stott et al. went on to state that in the absence of such adjustment, there is a statistically significant 45% excess risk of autism in recipients of the MMR vaccine and therefore, an apparent association between MMR and autism in this Danish population.

In addition, Stott et al. argued that a proper trend analysis would compare autism rates not by age at diagnosis but rather by date of birth. They obtained data from the same registry used by the authors that showed a clear upward trend in autism rates in birth cohorts born after the introduction of MMR in Denmark (see below).

## AUTISM PREVALENCE IN DENMARK BY BIRTH YEAR: 1982-92



**Prevalence in Denmark by year of birth, 1982-1992. Annual growth rate before MMR was -0.5%, but rose to 14.8% after MMR introduction in 1986.**

Moreover, Stott et al. claimed that the authors of the Danish study had selected a particular adjustment to their population groupings that removed a total of 13 ASD cases from the vaccinated group and placed them in the unvaccinated group. This single adjustment reduced the relative risk of autism associated with MMR vaccination at the population level by 17%, from 1.26 to 1.09. Stott et al. claimed that if the authors had removed all cases diagnosed before two years of age from their risk analysis, the relative risk at the population level would have risen from 1.26 to 1.28.

And Blaxill added another commentary of his own: “I conclude that the authors’ conclusion is not warranted. In my opinion, the Madsen article is useful in many ways but it definitely does not rule out MMR as a cause of autism, particularly not in a subgroup of the affected children.”

### WHAT THE COCHRANE REVIEW SAID:

- Follow up on medical records terminated just one year after the last day of admission to the cohort. “Because of the length of time from birth to diagnosis, the Cochrane reviewers felt it became ‘... increasingly unlikely that those born later in the cohort could have a diagnosis.’”
- The study was judged to have a “moderate” probability of bias.

- Interpretation of the study was “made difficult by the unequal length of follow up for younger cohort members” and the “use of date of diagnosis rather than onset of symptoms for autism.”
- The study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.”
- There was inadequate description of exposures, such as vaccine content and schedules.
- The study suffered from “clearly missing unintended-event data” and many participants were missing for adverse event monitoring. Adverse event data were missing in up to 1-in-5 participants (20%).
- The study failed to provide descriptions of all outcomes monitored.

### **SUMMARY:**

Madsen et al. argue no effect of MMR vaccination on autism in Danish children and even suggest there might be a protective effect to MMR exposure. Unfortunately, their study is plagued with questionable methodological choices, unexplained data anomalies and biased adjustments. In any study that asks a fundamental question about relative proportions of exposure in affected vs. unaffected groups, accurate definitions and classifications of (a) exposure and (b) affected status are crucial to the validity of any conclusions drawn from the data. Numerous criticisms of Madsen et al. highlight a source of error in one or another of these classifications. Methodology questions aside, more straightforward approaches to the population data they report suggest an increased risk of autism in Danish children based on MMR exposure, especially when adopting a case-based approach rather than relying on person-years. A simple comparison of autism rates by birth year shows a clear increase in autism rates after the introduction of MMR in Denmark. These analyses demonstrate that frequent references made based on Madsen et al. regarding the safety of MMR are incorrect.

## **2) Neurologic Disorders After Measles-Mumps-Rubella Vaccination.**<sup>7</sup>

**Authors:** Annamari Mäkelä, MD, J. Pekka Nuorti, MD, and Heikki Peltola, MD,

**Publication & Date:** *Pediatrics*, November 2002

**Online at:** [www.pediatrics.aappublications.org/cgi/content/full/110/5/957](http://www.pediatrics.aappublications.org/cgi/content/full/110/5/957)

**Details:** This paper is often referred to as the “Finnish MMR Study”. The authors conducted a retrospective cohort study linking individual MMR vaccination data with a hospital discharge register among 535,544 children in Finland, aged 1-to-7 years old, who were vaccinated between November 1982 and June 1986 in Finland. The authors looked for changes in the overall number of hospitalizations for autism after vaccination throughout the study period and for hospitalizations due to inflammatory bowel disease for children with autism. For encephalitis and aseptic meningitis, they compared the number of events observed within 3 months after vaccination to the number of events in the subsequent 3-month intervals for 24 months.

**Results:** Of the 535,544 vaccinated children, 199 were hospitalized for encephalitis, 161 for aseptic meningitis, and 352 for autistic disorders (a rate of 6.7-per-10,000). In 9 children with encephalitis and 10 with meningitis, the disease developed within 3 months of vaccination, revealing no increased occurrence within this designated risk period. Because there is no specific “risk period” for autism following vaccination, the authors looked for changes in the number of hospitalizations for autism after MMR vaccination for the study as a whole. They found no clustering of autism hospitalizations, which ranged from 3 days to twelve and a half years. None of children with ASD had hospital visits for inflammatory bowel diseases.

**Authors’ Conclusions:** “We did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, or autism.”

### **WHAT CRITICS SAID:**

**F. Edward Yazbak, MD:** Makela *et al.* were so intent on shooting down Wakefield’s work that even in a paper titled “Neurologic disorders after MMR,” they found a way to mention that no hospitalized children with autism had IBD. But regardless of what Makela says, the fact is that the number of individuals who received assistance for IBD from the Social Security Institution in Finland doubled in nine years (from 9,737 in 1992 to 20,807 in 2001).

The whole study is based on ONE comparison. If the children in the first group developed symptoms of encephalitis and meningitis within two weeks of vaccination, then causation is implied (medically and medico-legally). In this case, a comparison with the control group is meaningless and the author’s conclusion is unwarranted.<sup>8</sup>

## WHAT THE COCHRANE REVIEW SAID:

- This study suffered from a “moderate” risk of bias.
- It was “weakened” by the loss of 14% of the original birth cohort and the effects of the rather long time frame of follow up. What the impact of either of these factors was in terms of confounders is open to debate.
- The long follow up for autism was due to the lack of a properly constructed causal hypothesis.
- The study failed to report complete vaccine identification information, including lot numbers, adjuvants, preservatives, strains, product and manufacturer.
- There was a lack of adequate description of exposure (vaccine content and schedules).
- The authors provided “inadequate” explanations for missing information, even though there were clearly missing unintended-event data on as many as 20% of the participants.
- The study had discrepancies in reporting of denominators and was classified to be at moderate risk of bias.

**What the IOM said:** The study suffered from one primary limitation: its exclusive reliance on hospitalization records. This made it impossible to identify children with ASD who were not hospitalized, but rather seen in an outpatient setting. The IOM went on to say that “While the authors stated that it is common in Finland for children with autism to be admitted to the hospital for observation and testing, a diagnosis of autism does not always involve hospitalization.”<sup>9</sup>

**What Science-Based Medicine.com said:** “Using ‘hospitalizations’ as criteria for finding children with autism (is) not a good way to find autism cases, I agree.”<sup>10</sup>

## SUMMARY:

The “Finnish MMR study” fails to make explicit the exact definition of ‘caseness’, particularly with respect to autism. The criticisms leveled at the study are crucially important in this respect. First, there is a failure to differentiate between autism per se, and the sub-group who are proposed to be at increased risk (i.e. those with regressive onset). There is also a degree of circularity in the statement that those whose encephalitis was ‘unrelated to vaccination’ were excluded. To deselect particular cases before analysis, on the basis of a proposed non-relationship between exposure and outcome is poor epidemiological practice. Further, it implies that decisions about causality were made after the event, on the basis of criteria which were not made explicit to the reader. At face value, the exclusion of these cases would appear to work\_in favor of those proposing a possible association between exposure and hospitalization; but this would only be the case if the lack of association was real. No evidence is presented which

allows formulation of an opinion on this. The most problematic factor, however, is in the assumption that children hospitalized 'for autism' somehow represent the very well defined group of children that are proposed to be at risk of an adverse event following vaccination. This assumption simply has no validity, and neither, therefore, do any conclusions based on data related to this group.

### **3) No evidence for a new variant of measles-mumps-rubella-induced autism.**<sup>11</sup>

**Authors:** [Fombonne E](#), [Chakrabarti S](#)

**Publication & Date:** *Pediatrics* October 2001

**Abstract Online at:** <http://www.ncbi.nlm.nih.gov/pubmed/11581466>

**Details:** A link had been hypothesized between MMR vaccine and a type of ASD where developmental regression and gastrointestinal symptoms appear shortly after vaccination. The hypothesis involves 3 claims: 1) this is a new type of ASD, 2) this new type is responsible for the reported ASD rate increase, and 3) this new type is associated with symptoms suggestive of persistence of measles infection. If such a new "autistic enterocolitis" syndrome had some validity, then 1 or more of the following 6 predictions should be supported by empirical data:

- 1) Childhood disintegrative disorder has become more frequent
- 2) The age of first parental concern for ASD children exposed to MMR is closer to the average age of vaccination than in non-exposed children
- 3) ASD regression autism has become more common in MMR-vaccinated children
- 4) The age of onset for regressive ASD clusters around the MMR and is different from that of autistic children without regression.
- 5) Children with regressive autism have distinct symptom and severity profiles
- 6) Regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder.

The authors used three samples. Data on 96 children (95 immunized with MMR at a median age of 13.5 months) in the UK who were born between 1992 and 1995 and had a PDD diagnosis were compared with data from two other clinical samples (1 pre-MMR [n = 98] and 1 post-MMR [n = 68]) of patients with autism. Reliability was excellent on Autism Diagnostic Interview-Revised (ADI-R) scores, age of parental concern, and developmental regression. Data on bowel symptoms were also available from pediatric and parental sources, while vaccination dates were obtained from computer records.

**Results:** The authors state that prevalence of childhood disintegrative disorder was 0.6-per-10 000 – a very low rate, consistent with other estimates, and not suggestive of an increased frequency of this form of pervasive developmental disorder in samples of children who are immunized with MMR. Meanwhile there was no difference in the timing of first parental concern between the two MMR-exposed samples (19.3 and 19.2 months) and the pre-MMR sample (19.5 months). “Thus” the authors claim “MMR immunization was not associated with a shift toward an earlier age for first parental concerns.

Meanwhile, the proportion of children with developmental regression reported in the post-MMR sample (15.6%) was no different from the pre-MMR sample (18.4%); and



there was no suggestion that ASD regression had increased in frequency since MMR was introduced. The authors note that children with regressive ASD had no other developmental or clinical characteristics, a finding which, they claim, would have argued for a specific, etiologically distinct phenotype. Parents of regressive ASD children detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months), and the difference in time between MMR vaccination and parental recognition was not significant (248 vs. 272 days). GI symptoms were reported in 18.8% of cases, with constipation the most common (9.4%).

No inflammatory bowel disorder was reported, nor was there any association between regression and GI symptoms. Only 2.1% of the sample had both GI symptoms and regression, “a rate (sic) that did not exceed chance expectations.”

**Author’s Conclusions:** “No evidence was found to support a distinct syndrome of MMR-induced autism or of ‘autistic enterocolitis’,” and the study adds to “large-scale epidemiologic studies that all failed to support an association between MMR and autism at the population level.”

#### WHAT CRITICS SAID:

Critics question the basic assumptions behind the hypothesis, namely that if ‘autistic enterocolitis’ is real, then one or more of the authors’ six predictions would be borne out by the data.

■ **Prediction (1)** - "*childhood disintegrative disorder has become more frequent*". According to the study, the prevalence of childhood disintegrative disorder was very low, 0.6/10,000, and therefore had *not* become more frequent. But that figure is many times lower than estimated prevalence of regressive autism found in other studies, suggesting that the two cannot be equated.

■ **Prediction (2)** - "*the mean age of first parental concern for autistic children who are exposed to MMR is closer to the mean immunization age than in children who are not exposed to MMR.*"

The mean age at first parental concern was 19.3 months in the two MMR samples and 19.5 months in the pre-MMR sample. But just because one might expect to find a difference, the similar results do not really prove anything. For example, children in the pre-MMR sample were still exposed to live virus from monovalent measles.

■ **Prediction (3)** - "*regression in the development of children with autism has become more common in MMR-vaccinated children.*" The study found that regression in MMR-vaccinated children was no more common than regression in the pre-MMR sample, and had not increased in frequency. Furthermore, the children who did regress were no more likely to have other developmental or clinical characteristics, which would have supported the argument for a distinct regressive ASD phenotype.

The problem here is that the samples were quite small: two MMR-exposed samples of 96 and 68 children and one pre-MMR sample of 98. With numbers this small, only a few cases either way would have impacted the results.

■ **Prediction (4)** - *"the age of onset for autistic children with regression clusters around the MMR immunization date and is different from that of autistic children"*. The study found that parents of autistic children with developmental regression detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months). The study also found that the mean intervals from MMR to parental recognition of autistic symptoms were comparable in autistic children with or without regression (248 days vs. 272 days, not significant).

Vaccine-induced regression would not necessarily be expected to cluster around the time of MMR vaccination, but could be delayed by weeks, months, or even years in some individuals. There is no reasonable scientific justification to believe the children who regressed following MMR should be recognized at a different time than those who did not regress after the vaccine. And though the difference was deemed to be “not significant” (248 vs. 272 days) it is still an unexplained margin of 10%.

■ **Prediction (5)** - *"children with regressive autism have distinct symptoms and severity profiles."*

Not enough is known about ‘autistic enterocolitis’ to make such an assumption about external characteristics into a key test.

■ **Prediction (6)** - *"regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder"*.

It is impossible to say that none of these children had signs of inflammatory bowel disorder because none of them underwent colonoscopy.

#### **WHAT THE COCHRANE REVIEW SAID:**

- This study was assessed as having a “high likelihood” of bias.
- In fact, the number of biases and their likelihood to negatively impact the study “was so high that interpretation of the results was impossible.”
- The population description in this study raised doubts about the generalizability of the conclusions to other settings.
- This study failed to report complete vaccine identification information, including lot numbers, adjuvants, preservatives, strains, product and manufacturer.
- There was a lack of adequate description of exposure (vaccine content and schedules) in the study.

- This study failed to report any vaccine strains at all and failed to provide descriptions of all outcomes monitored.

**SUMMARY:**

The Fombonne and Chakrabarti study is flawed in a variety of ways. The biggest weakness is in its misinterpretation of the actual hypothesis of an association between a specifically defined sub-group of children and the exposure (MMR) of interest. It is on this erroneous understanding that the authors' assumptions are based. The assumptions are not valid and any findings based on them are consequently of little interest. The inadequate study design (in terms of poor definitions of cases, controls and exposures) also means that any other uses to which the data might be put are extremely limited.

#### **4) MMR vaccination and pervasive developmental disorders: a case-control study.**<sup>12</sup>

**Authors:** Smeeth L, et al.

**Publication & Date:** *Lancet*, September 11, 2004;364:963-9

**Abstract online at:** <http://www.ncbi.nlm.nih.gov/sites/entrez>.

**Details:** The authors conducted a matched case-control study using the UK General Practice Research Database. They included children born in 1973 or later who were diagnosed with a pervasive developmental disorder at a GP physician setting between 1987 and 2001. Controls were matched on age, sex, and general practice.

**Results:** 1,294 cases and 4,469 controls were included. Of the PDD cases, 1,010 (78.1%) received the MMR vaccine before their recorded diagnosis, compared with 3671 controls (82.1%) before the age at which their matched case was diagnosed. After adjustment for age at joining the database, the odds ratio for association between MMR and pervasive developmental disorder was 0.78 for the non-practice matched control group and 0.86 for the practice matched control group. Once again, the vaccine apparently had a protective effect: MMR vaccinated children were 22% less likely to have PDD compared with the non-practice matched control group and 14% less likely to have PDD than the practice matched control group. “Findings were similar when restricted to children with a diagnosis of autism, to those vaccinated with MMR before the third birthday, or to the period before media coverage of the hypothesis linking MMR with autism.

**Authors’ Conclusions:** “Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders.”

#### **WHAT CRITICS SAID:**

- Problems in the study design operate against the probability of detecting an increase in risk.
- There are significant changes from the methodology first proposed and subsequently cited in the present paper. Critics say it was crucial that case groups comprised only regressive, or late-onset, PDD, but Smeeth et al. confess (on p 967) that they were unable to do this.
- The small sample size is an issue – In order to complete such a matched-pair study with an estimated control exposure rate of 80%, the appropriate sample size would be 7,145 cases - almost six times the number of cases used in Smeeth et al.
- Two failings (below) in particular are “of such significance as to invalidate the conclusion that MMR vaccine is not associated with onset of autism in children.” (Wakefield)

- The authors state that they were “not able to separately identify the subgroup of cases with regressive symptoms to investigate the hypothesis that only some children are vulnerable to MMR-induced disease and that this is always regressive. In this single statement they make it clear that they have not conducted an investigation of “what has been referred to as ‘the Wakefield hypothesis.’”
- The paper “cannot be said to have concluded anything of relevance to the (Wakefield) hypothesis and has been grossly over-interpreted.
- Despite the authors’ assurance that all diagnoses would be validated by a detailed review of hospital letters and information from parental questionnaires, only 25% of cases had their records examined and no questionnaire was used.
- Other “substantial changes in the methodology” were also not explained in the paper, which therefore “meets neither the criteria for testing the original question nor those laid-down by the authors themselves.”

#### **WHAT THE COCHRANE REPORT SAID:**

- Although the study “appeared to be carefully conducted and reported,” the database used “had no unexposed (to MMR) representative controls.” And though the 4% to 13% figure of unexposed controls was regarded by the authors as “representative,” such small numbers “may indicate some bias in the selection of controls.”
- This underrepresented control “problem appeared to provide the rationale for the design of DeStefano 2004” (another study reviewed by Cochrane).
- In this study, it was “impossible” to determine the “precise nature of controlled unexposed to MMR and its generalizability.”
- This study suffered from a “moderate” risk of bias.
- This study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.
- This study failed to report any vaccine strains at all.
- The authors provided “inadequate” explanations for missing information, even though there were “clearly missing unintended-event data” on as many as 20% of the participants.

#### **SUMMARY:**

The Smeeth et al. study goes a step further in highlighting the inadequacy of study designs that fail to isolate the correct case-group by specifically stating their intention to

do so, (in a pre-study protocol discussion) and then clearly informing the reader that they failed to deliver on this intention. This represents a fundamental and fatal failure to address the right hypothesis. This means, in turn, that the study fails to add any data of scientific value regarding the vaccine-autism hypothesis whatever its other features might be.

**5) “Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta.”<sup>13</sup>**

**Authors:** Frank DeStefano, et al.

**Publication & Date:** *Pediatrics*, February 2004

**Abstract online at:**

[www.ncbi.nlm.nih.gov/pubmed/14754936?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/14754936?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**Details:** The authors conducted a case-control study in metropolitan Atlanta, where 624 ASD case children were identified from multiple sources and matched to control 1,824 children on age, gender, and school. This study assessed the association between MMR vaccine and the onset of autism among three age strata: up to 18, 24 and 36 months. Vaccination data were abstracted from immunization forms required for school entry. Records of children who were born in Georgia were linked to Georgia birth certificates for information on maternal and birth factors.

**Results:** The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children. 70.5% of ASD cases and 67.5% of control children were given the MMR vaccine between 12 and 17 months of age. Similar proportions of case and control children were vaccinated before 18 or before 24 months. “No significant associations for either of these age cutoffs were found for specific case subgroups, including those with evidence of developmental regression.” More case (93.4%) than control children (90.6%) were vaccinated before 36 months, and this association was strongest in the 3- to 5-year age group.

**Authors’ Conclusions:** “Similar proportions of case and control children were vaccinated by the recommended age or shortly after and before the age by which atypical development is usually recognized in children with autism (i.e. 24 months). Vaccination before 36 months was more common among case children than control children, especially among children 3 to 5 years of age, likely reflecting immunization requirements for enrollment in early intervention programs.”

**WHAT CRITICS SAID:**

The authors did not discuss the causes of the present epidemic now affecting the United States, but “simply stated that the MMR was unlikely to be the cause of regressive autism because children diagnosed with autistic disorders in Atlanta, Georgia received their first MMR vaccine at about the same age as unaffected children.”<sup>14</sup>

DeStefano and colleagues performed a case-control study comparing age at first MMR vaccination in children from the Atlanta metro area (2). By 36 months of age,

significantly more cases with autism (93%) had received MMR than controls (91%)(Odds Ratio 1.49; 95% confidence interval [CI] 1.04-2.14). This association was strongest in the 3 to 5-year age group with an Odds Ratio of 2.34. Due to diagnostic delay, a significant proportion of this group had yet to be diagnosed with autism, potentially underestimating this risk. Moreover, in a subgroup analysis looking at children with different disease characteristics, they found a significant association between MMR vaccination by 36 months and autistic children with no evidence of mental retardation (IQ>70; OR 2.54 [1.20-5.00]). The odds ratios were increased to 3.55 in a subgroup analysis adjusted for birth weight, multiple gestation, maternal age and maternal education, thus strengthening the association between age-of-exposure to MMR and autism.<sup>15</sup>

### **WHAT THE COCHRANE REPORT SAID:**

- Even though the authors concluded there was “no significant difference” between cases and controls in the age at first vaccination up to 18 months and 24 months, more cases received MMR before 36 months, making the two group different in an important sense.
- This conclusion “showed bias in the enrollment of cases which may not be representative of the rest of the autistic population of the city of Atlanta, USA where the study was set.”
- This study offered “inadequate explanations” for missing data.
- This study had the highest rate of excluded cases – more than one-third of the total – among all studies reviewed by Cochrane.
- Reporting on vaccine coverage and the “structure of comparisons” in this study were unclear, “raising the possibility of bias.”
- This study suffered from a “moderate” risk of bias.

### **SUMMARY:**

The DeStefano et al. study contains a number of important methodological flaws. Notably, however, the study group showed significant differences between cases and controls in age at vaccination. To dismiss this as being unimportant simply on the basis of similar overall proportions of case and control children being vaccinated by the recommended age is careless at best; contrived at worst. This is one of the few studies where any attempt has been made to look at a group of children with regressive onset, and it is one of the few to have demonstrated differences in age of exposure between case and control groups. This provides direct support for a role of MMR in increasing autism risk. That this alone didn't raise questions and stimulate genuine discussion in the paper itself is striking.



**6) “Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.”<sup>16</sup>**

**Authors:** B Taylor, et al.

**Publication & Date:** [Lancet](#). 1999 Jun 12;353(9169):2026-9

**Abstract online at:**

[http://www.ncbi.nlm.nih.gov/pubmed/10376617?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/10376617?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**Details:** The authors studied children with autism born since 1979 who were identified from special needs/disability registers and special schools in eight North Thames health districts, UK. Clinical records were linked to immunization data from the child health computing system. Investigators looked for trend changes in incidence or age of diagnosis when MMR was introduced to the UK in 1988. Clustering of onsets within defined post-vaccination periods was investigated by the case-series method. The researchers also recorded information on bowel problems (when they exceeded 3 months in duration), onset of parental concern about the child’s development, and regression (if there was documented decline in the child’s development or parents reported loss of skills).

**Results:** We identified 498 cases of autism (261 of core autism, 166 of atypical autism, and 71 of Asperger's syndrome). There was a steady increase in cases by year of birth with no sudden "step-up" or change in the trend line after the introduction of MMR vaccination. There was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated. There was no temporal association between onset of autism within 1 or 2 years after vaccination with MMR. Developmental regression was not clustered in the months after vaccination. No significant temporal clustering for age at onset of parental concern was seen for cases of core autism or atypical autism with the exception of a single interval within 6 months of MMR vaccination.

**Authors’ Conclusions:** “The authors reported a significant increase in onset of parental concern at six months post vaccination. They argued that this may have been due to multiple testing, caused by an unclear causal hypothesis, and concluded that the evidence did not support an association with autism. “If such an association occurs, it is so rare that it could not be identified in this large regional sample,” they wrote.

**WHAT CRITICS SAID:**

- Older children, born in 1984-1986, also received the vaccine as part of the United Kingdom’s Catch-up campaign.

- The authors erroneously concluded that the rise in autism started several years before MMR was introduced and therefore had nothing to do with this vaccine. In fact a substantial number (n=36) of their cohort had formed part of the Catch-up campaign, and the step-up in autism occurred at precisely the time the first children received MMR vaccine in North London.
- In their defense, the authors claimed that review of the records in the older recipients of MMR had identified parental concerns before MMR vaccination. They used this argument as justification for interpretation of a graph which simply presented number of children with autism versus year of birth, and owed nothing to apparent expressions of parental concern.
- The authors tested the hypothesis of temporal clustering of age at diagnosis of autism in defined time periods post MMR vaccination, an analysis which, because of the considerable delay in diagnosis, is likely to bias towards a negative finding.
- Despite this, they still found significant clustering of diagnoses by 6 months post MMR.
- The authors tested a hypothesis and found a positive association.

#### **WHAT THE COCHRANE REPORT SAID:**

- The absence of unvaccinated controls limits the inductive statements that can be made from this study.
- The authors were “uncertain as to the power and generalisability of the findings from the single case-only design study.”
- “This study demonstrates the difficulties of drawing inferences in the absence of a non-exposed population or a clearly defined causal hypothesis.”
- This study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.”
- This study failed to report any vaccine strains at all.

#### **WHAT THE IOM SAID**

There was an association between bowel problems and developmental regression – with almost twice the rate of bowel symptoms found in the regressive population. Thirty-one of the 118 children [26 percent] with regression and 49 of the 351 children [14 percent] without regressive autism reported bowel symptoms. “Single and multivariable logistic regression models, however, showed no association with these factors and MMR vaccine.”

**SUMMARY:**

Taylor et al. is another study that set out to address the issue of vaccine exposure in the correct set of (regressive onset) children and found an association between exposure and age of onset (within 6 months of exposure) and between regressive onset autism and bowel disease – both factors of crucial importance to the Wakefield hypothesis. The fact that the authors report the findings, but fail to discuss their potential importance, devalues the paper substantially. In addition, the design was not one from which observations on causality could be made and should be considered a descriptive study. Nonetheless the study provides clear evidence to support further evaluation of the precise factors outlined by the Wakefield hypothesis as being key to the potential MMR-autism association

## 7) “No effect of MMR withdrawal on the incidence of autism: a total population study”<sup>17</sup>

**Authors:** Hideo Honda, Yasuo Shimizu, and Michael Rutter,

**Publication & Date:** *Journal of Child Psychology and Psychiatry*. June, 2005.

**Abstract online at:** <http://www.ncbi.nlm.nih.gov/pubmed/15877763>

**Details:** The authors studied cumulative incidence of ASD up to age seven for children born from 1988 to 1996 in Kohoku Ward, Yokohama, Japan. Japan is unique, because MMR was introduced in 1989 and discontinued in April 1993. ASD cases included all cases of pervasive developmental disorders according to ICD-10 guidelines.

**Results:** MMR coverage dropped considerably in Yokohama in the birth cohorts of 1988 through 1992, (because of safety concerns over the strain of live mumps virus being used), and not a single MMR vaccine was administered in 1993 or thereafter. “In contrast, cumulative incidence of ASD up to age seven increased significantly in the birth cohorts of years 1988 through 1996 and most notably rose dramatically beginning with the birth cohort of 1993.”

**Authors’ Conclusions:** “The significance of this finding is that MMR vaccination is most unlikely to be a main cause of ASD, that it cannot explain the rise over time in the incidence of ASD, and that withdrawal of MMR in countries where it is still being used cannot be expected to lead to a reduction in the incidence of ASD.”

### CRITIQUES OF THE STUDY<sup>18</sup>

- The study tells us little about ASD incidence of ASD prior to 1988, when MMR was introduced. But we do know that the published *prevalence* of ASD did not exceed 25-per-10,000 at any time in Japan prior to 1988.
- Annual incidence of ASDs for children born in 1987 was 20-per-10,000, but after MMR was introduced, in 1988, annual incidence *more than quadrupled*, to 85.9-per-10,000 for children born in 1990.
- But then, MMR coverage began to decline dramatically, as concerns over the mumps viral component grew. ASD incidence likewise declined during this period, to 55.8 for children born in 1991 – representing a drop of 35%.

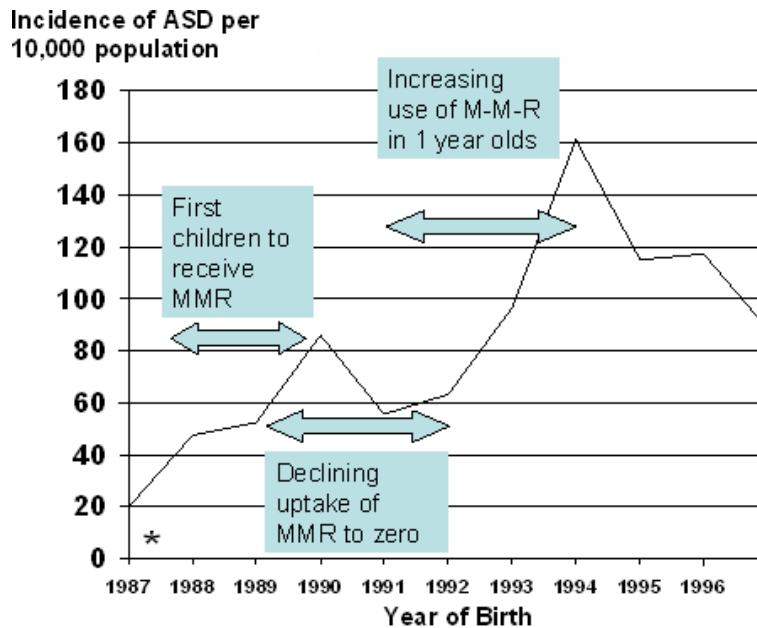


Figure 1. Annual trends in cumulative incidences up to seven years of childhood autism and other ASD

- Following complete discontinuation of MMR in 1993, ASD incidence rose again, this time quite dramatically, to 161-per-10,000 for children born in 1994. However, during this time the recommended schedule was changed to include three single vaccines (M-M-R, given four weeks apart), which gained widespread acceptance, causing coverage to increase significantly.
- For all practical purposes, children vaccinated according to the new schedule were still receiving 'M-M-R' at around age one. Giving the three separate vaccines in such close proximity amounts to overlapping exposure, in biological terms.
- Early MMR trials showed clear evidence of 'interference' between the viruses in the combined vaccine, mediated through an altered immune response. The safety consequences of this 'interference' are completely unknown.
- Children who have natural measles (or single measles vaccine) and natural mumps infections within the same year are at significantly greater risk of later inflammatory bowel disease,<sup>19</sup> which is consistent with an 'interference' phenomenon that could increase the risk of long-term measles virus infection and delayed disease.
- The authors are wrong to examine MMR as the single exposure of interest, when in biological terms, exposure to M-M-R through three consecutive monovalent vaccines actually increased after 1993 when MMR was discontinued.
- The data, therefore, could be interpreted as indicating a major influence of the pattern of exposure to these vaccine viruses on ASD incidence in this Japanese population.

- More importantly, the data suggest a possible re-challenge effect of close temporal exposure to these three vaccine viruses on ASD incidence at the population level, whereby the exposure (MMR) has been introduced, removed (voluntarily through lack of public confidence), and then re-introduced (as M, M, and R close together).

- ASD numbers increased and decreased in direct proportion to the total number of children vaccinated with the three live viruses. There is evidence of an effect not only from de-challenges and re-challenges, but there is also a “dose-response” relationship on a population level.

- Such a dose-response relationship on a population level is rare; and is evidence of a possible causal association.

- The interpretation by Public Health officials that this is the “last word on the subject” and that these data prove that MMR is safe is misleading and suggests a very limited perspective of the issues and a misunderstanding of published concerns on viral interference in a trivalent live-virus vaccine.

**Undisclosed Conflict of Interest:** Co-author Michael Rutter has close associations with the drug industry, including GlaxoSmithKline. He was a paid expert witness on their behalf in the UK MMR vaccine damage litigation. That was not declared in the Honda/Rutter paper.

#### **SUMMARY:**

Despite the methodological problems in Honda et al., and quite apart from the fact that an ecological study of this kind cannot be used to make attributions about causality, the unrecognized challenge-rechallenge effect of vaccination on autism rates in Japan provide yet another piece of support for the MMR-autism link. Because this study failed to clearly interpret the true population risk in the exposure of interest--assuming the removal of an exposure that in reality had remained-- the conclusions drawn by the authors are based on erroneous reasoning. Although drawing overly strong conclusions about an association between MMR-type exposures and autism would be premature in light of the study's ecological design constraints, the data clearly indicate that further scrutiny of the data is required.

## **8) “Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations.”<sup>20</sup>**

**Authors:** Eric Fombonne, MD, et al.

**Publication & Date:** *Pediatrics*, July 2006

**Online at:** <http://pediatrics.aappublications.org/cgi/content/full/118/1/e139>

**Details:** This cohort study surveyed 27,749 children born from 1987 to 1998 who went to 55 schools in the largest English-speaking school district in Montreal, Quebec. Children with PDDs (the Canadian term for ASD) were identified by a special needs team. The investigators looked at exposure to thimerosal by age 2 years and MMR coverage - which was estimated using vaccination rate surveys. The Canadian schedule called for an MMR injection at 12 months of age, up to 1995, when a second dose at 18 months was added.

**Results:** The authors found 180 children (82.8% of them males) with a PDD diagnosis at the surveyed schools, for a prevalence rate of 64.9 per 10,000. For autistic disorder, the rate was 21.6-per-10,000; for PDD-NOS it was 32.8-per-10,000; and for Asperger’s syndrome, 10.1-per-10,000. “A statistically significant linear increase in pervasive developmental disorder prevalence was noted during the study period,” the authors wrote. The PDD prevalence in thimerosal-free birth cohorts was significantly higher than among children who received thimerosal (59.5-per-10,000 vs. 82.7-per-10,000 – in other words, thimerosal-exposed children were 16% less likely to have an ASD).

Meanwhile, MMR coverage averaged 93% during the study period, though rates declined from 96.1% in the older birth cohorts (1988–89) to ~92.4% in younger birth cohorts (1996–1998). Thus, PDD rates “significantly increased” during the same period when MMR uptake rates “significantly decreased.” Moreover, PDD prevalence went up at the same rate before and after the second MMR dose was introduced in 1996, “suggesting no increased risk of pervasive developmental disorder associated with a 2-measles-mumps-rubella dosing schedule before age 2 years. Additional analyses to test for the potential effects of exposure or diagnosis misclassification yielded the same results.”

**Authors’ Conclusions:** PDD prevalence in Montreal was high, and increased in recent birth cohorts, as it had in most other countries. This rise was due to “a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification, (and) improved access to services.” There was no evidence that PDD had become more frequent, regression with autism had not become more common, and children with regressive autism did not have different profiles to those in the control group. These results “ruled out” an association between PDD and 1- or 2-dose MMR vaccinations.

### **WHAT CRITICS SAID**

■ Fombonne et al. evaluated children enrolled in only one of Montreal’s five school boards, Lester B. Pearson School Board (LBPSB), but they cautioned that PDD rates in

LBPSB may not have been representative of rates elsewhere and suggested that data from other school boards should be assessed but claimed, “this information was not available in the survey data that we could obtain.”

- Data from all five Montreal school boards was easily obtainable from the Ministry of Education of Quebec, and they showed that enrollment at LBPSB in 2003-04 represented only 14% of all total school board enrollments in Montreal, but the PDD rates were significantly higher than all four other school boards *combined*. In some cohorts, prevalence was three times higher in LBPSB than in other districts.<sup>21</sup>

- Fombonne et al. could not possibly have accurately estimated the citywide rates of PDD merely by assessing just this one school board; any conclusions about a relationship between vaccines and PDD rates in Montreal may be seriously flawed.

- By choosing to study only a small subset of the children in Montreal’s schools, the authors committed a serious selection bias.

- LBPSB includes a Center of Excellence in Autism, so its high rates of PDD are likely influenced by the fact that it is the only totally inclusive school board of the Province of Quebec and has a very high ratio of integration of students with PDD into regular classes. Many families of children with PDD often seek to enroll them in LBPSB resulting in an overestimate of true PDD rates in Montreal as a whole.

- Fombonne et al. chose to study MMR coverage rates, rather than the number of MMR vaccines received. He ignored the fact that autism rates increased following a doubling of the MMR exposure after 1996 when a second MMR shot was added to the schedule and chose to emphasize that a rise in PDD rates coincided with a decline in MMR coverage.

- Fombonne also ignored the possible effect of mass measles immunization campaigns in Quebec that delivered a second dose of measles to a large number of infants and children throughout 1996.<sup>22</sup> The subsequent rise in PDD shortly after that campaign is clearly depicted in their figures.

- MMR coverage data was taken from the city of Quebec, rather than from Montreal, where the PDD data was gathered. MMR data “were available through N. Bouliane, of the Direction de Santé Publique de la Capitale Nationale,” the authors wrote. But the “Capitale Nationale” refers to Quebec City, not Montreal, some 265 kilometers away. Ms. Bouliane confirmed that the MMR vaccination rates were from the Quebec City.

- Published MMR vaccine surveys from Montreal show that rates among children 24 to 30 months old did not fall during the period in question, but actually increased from 85.1% in 1983 (Baumgarten)<sup>23</sup> to 88.8% in 1996-97 (Valiquette)<sup>24</sup> to 96% in 2003-04 (Health Department Survey).<sup>25</sup>

- This suggests that in Montreal, PDD prevalence and MMR vaccination rates were in fact increasing in tandem during the study period.



■ F. Edward Yazbak, MD, FAAP, wrote to *Pediatrics* to protest,<sup>26</sup> and said that “Readers deserve to know why the authors compared developmental data from a specific group of children in Montreal with MMR vaccination data from the city of Quebec, some distance away.”

■ In response, Dr. Fombonne failed to address the criticisms when he wrote to the editor of *Pediatrics* that, “This person (Yazbak) is known to pursue the MMR-autism agenda at all costs in order to 'demonstrate' a link he strongly believes in. All controlled epidemiological research thus far has concluded to the absence of such a link.”<sup>27</sup>

■ The Editor of *Pediatrics*, Jerold F. Lucey, also wrote to Dr. Yazbak, and stated that “I believe the evidence of no link between MMR and Autism is sufficient. It's not worth publishing more on this subject.”

■ Dr. Yazbak subsequently stated: “I found and reported a glaring error in the paper. The rates of autism in Montreal have as much to do with MMR vaccination rates in Quebec City as pollution in Los Angeles with Diesel buses in Chicago. The lead author refused to respond to my criticism concerning that simple geographic fact and the editor was unable to force him to do so.”<sup>28</sup>

#### **SUMMARY:**

The criticisms of Fombonne are numerous and cover the most basic questions of study design, data quality, data interpretation and consistency. Furthermore, Fombonne's ad hominem attacks on his critics undermine his personal credibility. The single most ‘glaring error’ reported by Dr Yazbak, i.e. that “The rates of autism in Montreal have as much to do with MMR vaccination rates in Quebec City as pollution in Los Angeles with Diesel buses in Chicago”, undermines any of the conclusions drawn by the authors. That simple failure to match exposures and outcome is sufficient by itself to render its conclusions worthless.

## **9) “MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis.”<sup>29</sup>**

**Authors:** M. Vestergaard et al.

**Publication & Date:** *Journal of the American Medical Association*, July 21, 2004

**Abstract online at:** <http://www.ncbi.nlm.nih.gov/pubmed/15265850>

**Details:** MMR vaccination increases the rate of febrile seizures, though it is not known if the rate varies according to personal or family history of seizures, perinatal factors, or socioeconomic status, and little is known about the long-term outcome of febrile seizures following vaccination. The authors conducted a population-based cohort study of all children born in Denmark between January 1, 1991, and December 31, 1998, who were alive at 3 months. 537,171 children were followed up until December 31, 1999. While this study did not measure autism, its main outcomes studied were incidence of first febrile seizure, recurrent febrile seizures, and subsequent epilepsy.

**Results:** A total of 439,251 children (82%) received MMR vaccination and 17,986 of them developed febrile seizures at least once; 973 of these febrile seizures occurred within 2 weeks of MMR vaccination. The rate ratio (RR) of febrile seizures increased during the 2 weeks following MMR vaccination - (RR 2.75, or 175% more likely) and, after that period, were close to the observed RR for non-vaccinated children. The RR did not vary significantly in subgroups of children that had been defined by their family history of seizures, perinatal factors, or socioeconomic status. At 15 to 17 months, the risk difference of febrile seizures within 2 weeks following MMR vaccination was 1.56 per 1000 children overall, 3.97 per 1000 for siblings of children with a history of febrile seizures, and 19.47 per 1000 for children with a personal history of febrile seizures. Children with febrile seizures following MMR vaccinations had a slightly increased rate (19%) of recurrent febrile seizures (RR, 1.19) but no increased rate of epilepsy compared with children who were non-vaccinated at the time of their first febrile seizure.

**Authors’ Conclusions:** MMR was associated with a transient increased rate of febrile seizures but the risk difference was small even in high-risk children. The long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology.

### **WHAT THE COCHRANE REVIEW SAID**

- The rate of febrile seizures was significantly higher during the first week after vaccination (RR 2.46) and second week (RR 3.17) but not thereafter. Overall, MMR was associated with a higher risk of febrile seizures (RR 1.1).
- These are plausible conclusions given that MMR is a viral live attenuated vaccine. There appeared to be no association with a family history of febrile seizures but there was

a four-fold increase in risk of seizures within the first two weeks after MMR in siblings of children with epilepsy and a 19% increase in the risk of a second febrile seizure.

■ Overall, this was a well-reported, powerful study with credible conclusions as all possible efforts to account for confounders were made. This was the only cohort study judged to have a low probability of bias.

■ This study failed to provide descriptions of all outcomes monitored.

### WHAT CRITICS SAID

■ This was one of the best constructed studies reviewed by Cochrane and carried the lowest risk of bias of all 14 cohort studies. And though the paper did not look at autism, it did find that the risk of febrile seizures more than tripled (RR 3.17) in the second week after MMR vaccination.

■ This study's findings were consistent with other studies showing that MMR vaccination increases the risk of febrile seizures, causing them in 10-to-20-per-10,000 injections, and in 220-per-10,000 children with a previous history of febrile seizures.<sup>30</sup>

■ In 1994, a panel of the Institute of Medicine, writing about measles vaccine and brain injury or inflammation, concluded: "The National Childhood Encephalopathy Study, a case-control study described in detail in Chapter 5, reported a significant association between measles vaccination and onset of either convulsions or encephalopathy within 7 to 14 days of receiving the vaccine."<sup>31</sup>

■ MMR vaccine, when combined with varicella (chicken pox) live-virus vaccine into the 4-in-1 combination *ProQuad* shot, doubles the risk of seizures in children, compared with two separate MMR and chicken pox vaccines, a CDC study found. The CDC's Advisory Committee on Immunization Practices had recommended the vaccines be administered as separate shots, but subsequently voted to not recommend a preference between ProQuad and giving separate MMR and varicella vaccines. <sup>32</sup>

■ The MMR vaccine, (as well as DTP), is recognized by the US Department of Health and Human Services as a known cause of "encephalopathy" (brain disease) in a small subset of children. Acute encephalopathy induced by MMR exposure in children 18 months and older is associated not only with seizures, but can also cause a "decreased level of consciousness."<sup>33</sup>

■ "A significantly decreased level of consciousness" induced by MMR exposure is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:

**1) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli).**

Meanwhile “Many children with autism have a reduced sensitivity to pain, but are *abnormally sensitive to sound, touch, or other sensory stimulation,*” according to the National Institute of Neurological Disorders and Stroke (NINDS).<sup>34</sup>

**(2) *Decreased or absent eye contact (does not fix gaze upon family members or other individuals).***

“Children with autism often *avoid eye contact* with other people.”

**3) *Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).***”

“A baby with autism may be *unresponsive to people* or become indifferent to social engagement.”

■ In **Bailey Banks v HHS**, the Federal Vaccine Court ruled that Bailey’s case of Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) was a direct result of his development of acute disseminated encephalomyelitis (ADEM), a neurological disorder characterized by inflammation of the brain and spinal cord and damage to the myelin sheath, a fatty coating that insulates nerve fibers in the brain. Symptoms of ADEM include seizures. The judge ruled that Bailey’s ADEM was caused by his MMR immunization, “leading inexorably from vaccination to Pervasive Developmental Delay.”<sup>35</sup>

#### **SUMMARY:**

Verstergaard et al. was more effectively designed than most other MMR safety studies. This analysis, however, did not explicitly include autism as an outcome. Nevertheless, did find an increased risk of febrile seizure following MMR, a finding that is consistent with other studies of MMR. The similarities between the Bailey Banks case--one in which the U.S. government conceded that a febrile seizure after MMR resulted in brain inflammation and an autism spectrum disorder--and the findings reported in this paper are striking. The dismissal of concerns over an adverse event like a febrile seizure highlights the casual and careless manner in which potentially crucial evidence is interpreted.

## **SOME FINAL REMARKS FROM CRITICS OF EPIDEMIOLOGICAL STUDIES ON MMR AND AUTISM**

(The following quotes were part of official presentations made on February 9, 2004 to the Vaccine Safety Committee of the Institute of Medicine.)<sup>36</sup>

“The current genetic research estimates that no more than 10% of all autistic cases are genetic in origin. Simply put, the remainder 90% of autistic cases is sporadic with a non-genetic etiology. I tend to think that the sporadic form is by and large an “acquired” subset involving autoimmunity. This subset is likely triggered by a virus, possibly measles virus or MMR vaccine. Based upon our experimental research, it is plausible to postulate that an atypical measles infection that does not produce a typical measles rash but manifests neurological symptoms might be etiologically linked to autoimmunity in autism. The source of measles virus could potentially be MMR vaccine or a mutant measles strain, but more research is necessary to establish either of these two possibilities.” -- **Vijendra K. Singh, Ph.D., Research Associate Professor of Neuroimmunology, Utah State University, an international expert in the autoimmune causes of autism.**

”Half of Dr. Wakefield’s theory has been proven correct and accepted in the medical community. Hundreds of children with regressive autism and GI dysfunction have been scoped and clinicians are seeing the inflammatory bowel disease he first described.” -- **(Fmr) U.S. Representative Dave Weldon, MD (R-FL).**

“In light of encephalopathy, presenting in children as autistic regression closely following MMR vaccination. The findings confirm a highly significant statistical association between the presence of measles virus RNA in cerebral-spinal fluid and autistic regression following MMR vaccination.” -- **Jeff Bradstreet, MD, Director, International Child Development Resource Center.**

## **PART 3**

### **FLAWS AND LIMITATIONS OF THIMEROSAL-AUTISM EPIDEMIOLOGY STUDIES**

There has only been one major scientific review of the main epidemiological studies to examine a potential association between thimerosal containing vaccines (TCVs) and autism spectrum disorders: The Institute of Medicine Immunization Safety Committee Report, issued in May, 2004.<sup>37</sup>

The IOM report focused almost exclusively on large, population-based epidemiological studies based on health records. The committee chose to minimize the importance of several biomedical thimerosal studies conducted in laboratories and animal models. Today, a much larger body of medical literature has been amassed which clearly demonstrates the powerful neurotoxic effects of thimerosal. These are joined by other studies demonstrating the increased risks of simultaneous administration of certain vaccines on the current childhood schedule.

#### **WHAT THE IOM CONSIDERED:**

The IOM committee reviewed epidemiological studies examining TCVs and autism, including three controlled observational studies (Hviid et al., 2003; Miller, 2004; Verstraeten et al., 2003) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003). The published papers “consistently provided evidence of no association between TCVs and autism, despite the fact that these studies utilized different methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom),” the committee wrote.

#### **IOM MAIN CONCLUSIONS:**

- “Based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.”
  
- “In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.”

#### **LIMITATIONS OF THE IOM REVIEW:**

- Because the “vast majority” of ASD cases cannot be accurately sub-classified, “if there is a subset of individuals with autism syndrome triggered by exposure to vaccines, our ability to find it is very limited in the absence of a biological marker.”

■ In fact, the committee admitted, trying to find a cause of autism using population-based epidemiological analyses “requires either a well-defined at-risk population or a large effect in the general population.”

■ But without any known biomarkers, well-defined risk factors, or large effect sizes, “the committee cannot rule out, based on the epidemiological evidence, the possibility that vaccines contribute to autism in some small subset or very unusual circumstances.”

*NOTE: Knowledge of biomarkers and risk factors in ASD has increased considerably since the release of the 2004 IOM report.*

## **CRITIQUES OF THE IOM REVIEW**

**Mark D. Noble, PhD - Professor of Genetics and of Neurobiology and Anatomy, University of Rochester Medical Center**<sup>38</sup>

It is easy to understand why people are not believing the scientific community. It reduces confidence in the scientific enterprise when it turns out that the CDC had information on early versions of the studies of Verstraeten et al. that demonstrated a linkage between thimerosal exposure and autism, that these studies were never published, and that no one has ever explained satisfactorily why different analyses were conducted and why they were changed. But all of these studies have equally debilitating flaws that invalidate any conclusions drawn from them on thimerosal safety. And if it turns out that there is a subset of children for whom additives in vaccines are a problem, then this is important to know. For then we can focus on how to identify these children in advance. The conclusions I have drawn are that we are not going to solve this problem by ignoring it. So let's embrace it. Let's get the data.

**Irva Hertz-Picciotto, PhD, MPH, Chief of the Division of Environmental and Occupational Health, University of California, Davis School of Medicine** –<sup>39</sup>

Several large studies finding no association are far from robust, as they suffer from numerous biases that seriously limit their definitiveness. These include: noncomparable sources for ascertainment of cases, uncontrolled confounding, unrepresentative sample due to selective exclusions, and an as-yet unexplained pattern whereby children with earliest vaccines are the least likely to have developmental deficits. Thus, the body of evidence at this point is inadequate to draw conclusions... Several investigations have been ecologic studies, widely known to be the weakest possible epidemiologic design. Even restricting discussion to the individual-level designs, published studies conducted in Denmark, the UK, and the US are characterized by serious, even fatal, flaws. To regain the confidence that we in the medical/public health/scientific community need in order to fulfill our mandate to protect health, we cannot avoid facing these tough scientific questions head-on. This means funding solid scientific

research into vaccines, thimerosal, and the related issues of susceptibility at the population level.

**Richard Deth, PhD, Professor of Pharmacology, Northeastern University –  
40**

The report aims to close the door on concerns that mercury-containing vaccines might have contributed to the increased frequency of autism. Unfortunately it is obvious that the need to close the door was given a higher priority than reaching reliable scientifically-based conclusions. This is particularly evident when the report shockingly takes a hard-line against further research into this important question ... From the very outset, (IOM committee chairwoman) Dr. Marie McCormick displayed a pugnacious and adversarial attitude toward the presentation of information suggesting a thimerosal/autism link, as opposed to that of a neutral investigator... The report reflects a similar adversarial tone, with a welcoming, uncritical presentation of those epidemiological studies which failed to find a link contrasted to a hypercritical, dismissive approach toward data supportive of a link. The IOM clearly valued the epidemiologic approach and de-valued results derived from autistic individuals. The report was a biased effort at damage control.

**Dr. Joachim Mutter, FA, Institute for Environmental Medicine and Hospital Epidemiology, University Hospital Freiburg, Germany and US and UK colleagues –<sup>41</sup>**

Epidemiological studies which do not consider genetic susceptibility factors, autoimmunity reactions and mercury exposure during pregnancy (amalgam, thimerosal), are not able to detect a statistically significant effect, even if there is one. (NOTE: *None* of the epidemiological studies reviewed by the IOM committee considered any of those factors.)

**Rep. Dave Weldon, MD (Congressman from FL at the time) –<sup>42</sup>**

Today's report is premature, perhaps perilously reliant on epidemiology, based on preliminary incomplete information, and may ultimately be repudiated... Unfortunately, the epidemiology studies that the IOM bases its findings on are not immune from conflicts or controversy. Many of the authors have conflicts of interest including funding from vaccine manufacturers, employment by manufacturers, or conflicts in that they implemented vaccine policies that are now being investigated. Furthermore, the studies were designed to examine entire populations and would miss subgroups of genetically susceptible populations.

**Boyd Haley, PhD, Professor of Chemistry and Bioorganic Chemistry,  
University of Kentucky –<sup>43</sup>**



It appears very solid that autistic children do not biochemically handle mercury as do normal children. This is not theoretical, this is biochemical fact -- the IOM members just chose to ignore it as it does not fit into what they wanted to report. (Some) data clearly show that a small subset of the population is being affected by mercury that would be somewhat difficult to detect with a less than elegantly designed epidemiological study, and easy to miss or cover up. This biochemical data does not totally prove thimerosal is causal for autism, but it certainly should have prevented the IOM from saying they 'conclusively' proved thimerosal was not involved. If you do not believe in a hypothesis you replace it with another. That is how science is done.

#### **Coalition for SafeMinds – 44**

This committee clearly chose to ignore groundbreaking scientific research on the mercury-autism link, and instead the IOM has issued a flawed, incomplete report that continues to put America's children at risk. The problem with this report begins with its violation of nearly every tenet of medical science. Respected researchers everywhere do not support the IOM belief that proof can be solely found in epidemiology... Disclosure of potential conflicts of interest is an essential tenet to good science, but here we have a situation where authors of 'studies' are probably quite literally writing to preserve their jobs. The IOM gave unusual weight to several authors from the Statens Serum Institut (SSI) in Denmark. What the American public needs to know is that the SSI is not only the Danish version – and frequent collaborative partner – of the CDC, but also that country's largest vaccine manufacturer.

#### **WHAT IOM COMMITTEE MEETING MINUTES SUGGEST:**

On January 12, 2001, the IOM's Immunization Safety Review Committee held a closed-door meeting convened by Committee Chairwoman Dr. Marie McCormick and Study Director Kathleen Stratton. During the meeting, members discussed their charge from the CDC, which commissioned the review. The minutes were leaked to attorneys for families of children with autism.<sup>45</sup>

At one point, Dr. McCormick seems to imply that CDC officials expect certain pre-ordained results from the study they are sponsoring and paying for:

**Dr. McCormick:** "CDC wants us to declare, well, these things (vaccines) are pretty safe on a population basis."

And Dr. Stratton announces to the committee what they WON'T be finding or recommending, before a single page of evidence has been presented:

**Dr. Stratton:** "The point of no return, the line we will not cross in public policy, is pull the vaccine, change the schedule. We could say it is time to revisit this, but we would never recommend that level. Even recommending research is

recommendations for policy. We wouldn't say compensate, we wouldn't say pull the vaccine, we wouldn't say stop the program.”

Later, Dr. McCormick also announces a predetermined finding:

**Dr. McCormick:** “We are not ever going to come down that [autism] is a true side effect.”

**SUMMARY:** The IOM Committee gave far more emphasis to epidemiological (population based) studies than biological studies, such as clinical studies in children, laboratory studies, and animal model studies. Since the IOM report was released in May, 2004, a large amount of biological data have been generated from several published studies to support an association between thimerosal and ASD. A new IOM review that includes these studies is needed.

## INDIVIDUAL THIMEROSAL STUDIES

### 1) “Autism and thimerosal-containing vaccines: lack of consistent evidence for an association.”<sup>46</sup>

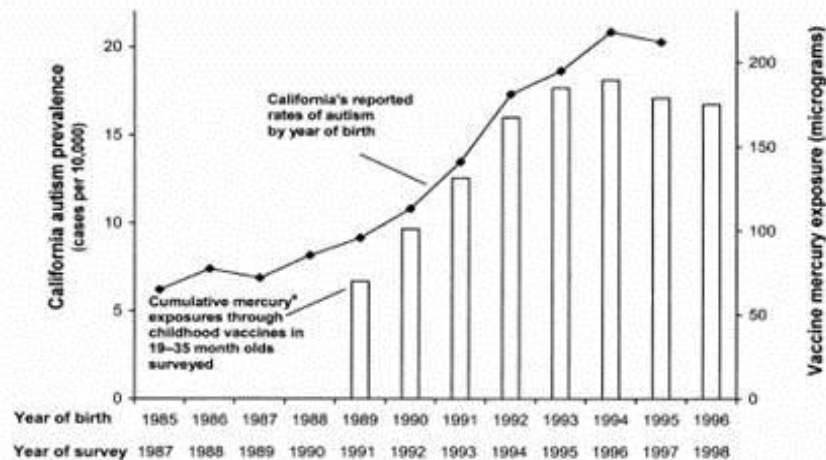
**Authors:** Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D.

**Publication & Date:** *American Journal of Preventive Medicine*, August, 2003

**Abstract online at:** <http://www.ncbi.nlm.nih.gov/pubmed/12880876?dopt=Abstract>

**Details** The authors compared thimerosal exposures and autism rates among children in Denmark, Sweden, and California. In California thimerosal use in childhood vaccines had continued until 2003, while Sweden and Denmark eliminated it in 1992-1993.

**California** - The authors examined data that SafeMinds member Mark Blaxill had presented to the IOM Immunization Safety Committee in June, 2001, which showed a time correlation between rising exposure levels and rising case numbers. But “as with most ecologic analyses,” they wrote, “the data that Blaxill had compiled had several limitations.” For example, the autism definition used by the California Department of Developmental Services (DDS) was somewhat “vague” and difficult to verify, the authors said. Any reported increase might have been caused by greater awareness and changes in diagnostic criteria, including the addition of autistic related illnesses, such as Pervasive Developmental Disorder (PDD), the study asserted, adding that, “These subcategories of PDD accounted for the largest increases in the reported California cases reflected in the data used.”



**Sweden** – The authors reported that autism rates continued to climb after thimerosal was removed from Swedish pediatric vaccines in 1993. Looking only at autism patients in Sweden who were diagnosed in an inpatient (hospital) setting, they found that autism numbers rose and fell in an erratic pattern during 1980-1997, but still had an upward trend over the period. Case rates went from 5 or 6 cases “per 100,000 person-years” before 1985, to a peak of 9.2 per 100,000 person years in 1993. “This was generally similar to the trend in California during the same time period,” the authors said:

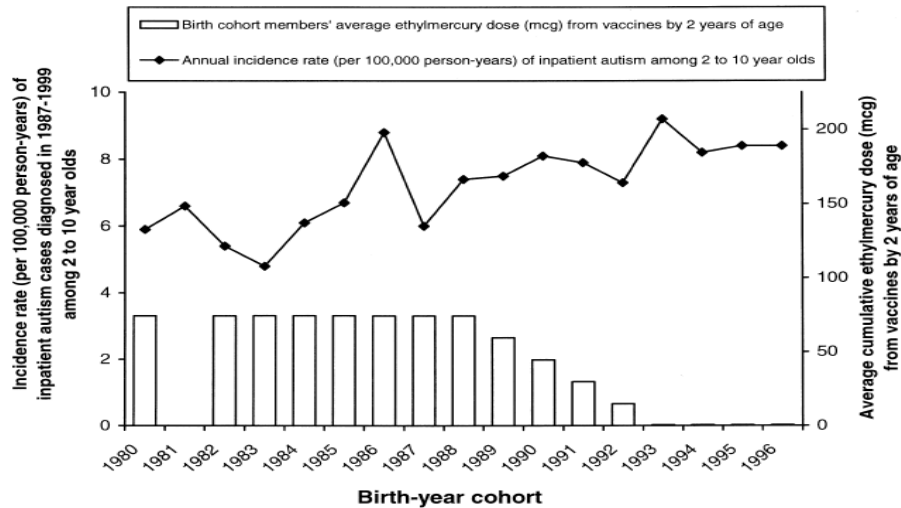
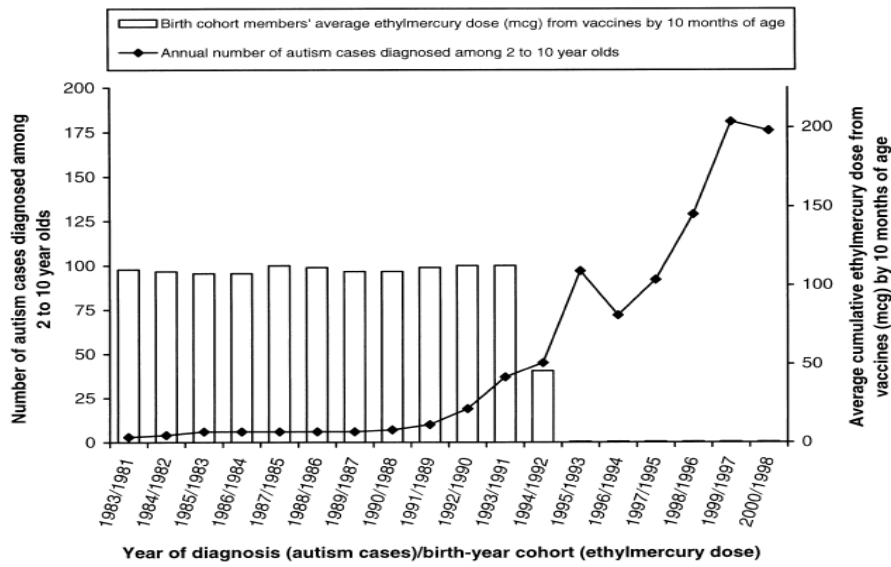


Figure 2. Graphical ecologic analysis comparing average cumulative ethylmercury dose received from vaccines and the incidence rate (per 100,000 person-years) of autism cases in children aged 2 to 10 years diagnosed during 1987-1999 in inpatient settings in Sweden, by birth-year cohort from 1980 to 1996. (Data not available for year 1981.)

**Denmark** - Case rates in Denmark also went up after thimerosal was removed, in 1992. But this increase was linear, and much more pronounced. Prior to 1992, Danish children were exposed to up to 125 micrograms mercury by age ten months, but reported autism rates during this period remained level, at about 10 new cases a year. By 1999, however, after thimerosal was removed, the reported number of new autism cases had climbed to about 200 – an astonishing 20-fold increase.



**Figure 3.** Graphical ecologic analysis comparing the average cumulative ethylmercury dose received from vaccines by birth-year cohort from 1981 to 1998, and the annual number of incident cases of autism in children aged 2 to 10 years diagnosed in Denmark from 1983 to 2000.

**Results:** “In all three countries, the incidence and prevalence of autism-like disorders began to rise in the 1985-1989 period, and the rate of increase accelerated in the early 1990s,” the authors wrote. But ethylmercury exposure levels were significantly different. The average dose from TCVS increased throughout the 1990s in the United States, but in Scandinavia, thimerosal was removed in the early 1990s.

**Authors’ Conclusions:** Results from Scandinavia provided “compelling evidence in sharp contrast to the alleged association observed in California” against a thimerosal-autism association, the study said. “The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.” More plausible explanations for the increase included: “increased recognition of the disorder, and/or other as-yet-unidentified environmental or genetic factors.”

## CRITIQUES OF THE STUDY

Critics point to this study’s most glaring flaw, which appears in the Denmark section. The authors relied on autism prevalence data as reported in the Danish Psychiatric Central Register. But the way in which Denmark diagnosed and tracked autism patients had changed radically over the course of their investigation. This created an important alteration in the study’s entry criteria midway through the study period.

■ **Changing Danish Population** - From 1983-1992, the Danish register only listed autism cases that were diagnosed in an inpatient (hospital) setting. But in 1992 data from a large, state-of-the-art autism clinic in Copenhagen, which was diagnosing about 20% of all cases in the country was added to the national register. That year, the same year that

thimerosal was removed from childhood vaccines, the number of reported autism cases, not surprisingly, saw a significant spike.

■ **Adding Outpatient Cases** - In 1995, for reasons that went unexplained, the national register began including *all* autism cases diagnosed in Denmark, including those diagnosed in outpatient settings. Most people with autism are diagnosed in clinics and private offices, not in hospitals. SafeMinds and other organizations point to a large 2002 study in Denmark - on autism and the MMR vaccine by Madsen et al. (see MMR section) – showing that outpatient-diagnosed cases outnumbered inpatient cases by a 13.5-to-1 ratio in Denmark, accounting for 93% of all autism cases.<sup>47</sup>

■ **New Diagnostic Criteria** - A third change in methodology occurred during the study period as well. In 1993, Denmark updated its psychiatric diagnostic codes and adopted new diagnoses for autistic-related disorders. Government workers conducted training seminars with clinicians in order to promote the new coding system, and an increase in autism and other reported diagnosis was to be fully expected.

■ **Denmark: An Artificial Increase?** This study “manipulates the incidence of autism in an attempt to clear thimerosal-containing vaccines of any role in the etiology of the disease,” a SafeMinds said in a statement. The increase reported in Denmark was “falsely created by the authors’ use of techniques which artificially boosted the number of cases identified.”

■ **Sweden: Inpatient Cases Only** - By counting only inpatient cases in Sweden, the reliability of that country’s data is also called into question. This limitation (counting a minority of the total number of cases) likely accounted for the erratic swings in the annual numbers of autism cases reported in that country.

■ **California: Increase is Real** - Sterh-Green et al. erred by writing that California’s Department of Developmental Services used a “vague” and difficult to verify autism definition. Their speculation that “changes in diagnostic criteria,” including PDD, “accounted for the largest increases” is not supported by the evidence. California’s data included only full-blown cases of autism, and not PDD. If anything, diagnostic criteria for “classic” autism became *narrower* over the years. And the suggestion that changes in criteria or “diagnostic substitution” (from mental retardation to autism) could explain the reported 800% increase in California has been disproven in several published papers. No retraction or correction of the authors’ erroneous claims was made.

## WHAT THE STUDY SAID

■ **Inpatient v Outpatient Cases** - The authors noted that the switch from counting inpatient cases only, to counting all cases “Changes over time in the rates of diagnosis of autism-like disorders in inpatient versus outpatient settings may have affected the ascertainment of cases,” the authors said, adding that these very significant changes “may have spuriously increased the apparent number of autism cases.”

■ **Weakness of Ecological Studies** - The authors also noted the inherent weaknesses of relying on large epidemiology investigations called “ecological” studies, in which the unit of analysis is a population group and not individuals. They conceded that these studies are inherently limited in their ability to prove or disprove causation. “Such studies can be useful in exploring possible associations, (and) searching for areas of possible further study,” they wrote. “However, the greatest difficulty in interpreting ecologic studies is that of adequately controlling confounding factors due to unavailability of data and/or methodological limitations.”

## **WHAT THE CDC SAID ABOUT ECOLOGICAL STUDIES**

An unpublished 2008 report from the CDC to the US House of Representatives Appropriations Committee concurs that ecological studies are far from ideal when using computerized population data - in this case the federal Vaccine Safety Datalink (VSD) - to determine an association between vaccines and autism.<sup>48</sup>

“CDC concurs that conducting an ecologic analysis using VSD administrative data to address potential associations between thimerosal exposure and risk of AD/ASD is not useful,” said the CDC paper, which was signed by then Director Julie Gerberging, MD, now President of the Vaccine Division at Merck & Co., Inc. Such an evaluation, she added, “would be uninformative and potentially misleading.”

## **WHAT THE IOM COMMITTEE SAID:**

■ **Shifting Study Population** – In its 2004 report, the Immunization Safety Review Committee agreed that “possible reasons” for the autism increase in Denmark “may be due to the changes in the inclusion criteria in the national register, diagnostic changes (from ICD-8 diagnostic coding to ICD-10), and the fact that, prior to 1992, cases diagnosed in one large clinic (about 20 percent of all cases) were not included.”

■ **Weakness of Ecological Studies** - The committee likewise conceded that “The ecological nature of the study limits the study’s contribution to causality.”

■ **Swedish Contribution is Limited** - As for the Swedish data, “which only reflected cases diagnosed in inpatient settings” the IOM committee admitted that the reported increase might have been caused by “changes in diagnostic criteria and increasing awareness of autism and related disorders.” The Sweden section, likewise, was an ecological analysis, which again “limits the study’s contribution to causality.”

## **CRITIQUE BY MARK D. NOBLE - PROFESSOR OF GENETICS AND OF NEUROBIOLOGY AND ANATOMY, UNIVERSITY OF ROCHESTER MEDICAL CENTER<sup>49</sup>**

One hypothesis to explain the sudden increase in prevalence is that changes in diagnosis and increased interest in autism caused an enhanced recognition of children with these syndromes. Thus, we know that the reported prevalence

from 1971 to 1990 is artificially low, because it doesn't include children who were given a different diagnosis. That means that in its current form, the comparison between the 1971-1990 cohort and later cohorts is fundamentally flawed, because they represent different kinds of information. There is quite an explosive change that is going on between 1995 and 2000. What could explain this? When you read the actual details of this manuscript (Madsen et al., 2003) you find out that, in 1995, a change was made in the information contained in the Danish registry. Prior to 1995 this registry only contained inpatient data, but after 1995 it also included data from outpatients.

In fact, the paper states that this change introduced 4-6 times as many total individuals into the registry. But it did not increase for a biological reason – it increased because they simply were obtaining cases from 4-6 times as many total people. At least in the years 1991-1998, 93.1% of the autism cases were treated only as outpatients. Thus, the addition of outpatients to the analysis in 1995 may have added 13.5 times as many cases of autism to the number of cases reported. If we apply even the most conservative correction factor for non-biological contributions, then a reasonable interpretation ... is that the biological prevalence of PDD fell by 30-40% after the removal of thimerosal from vaccines. Even the application of the lower end of the possible correction factors leads to the conclusion that there was a fall in autism prevalence after thimerosal was removed from vaccines.

**SUMMARY:** This weak review analyzed data from three different countries where mercury exposures were vastly different, and where autism cases were counted in very different ways. In addition, over the study period, the Danish autism registry switched from counting only inpatient-diagnosed cases (about 13% of the total) to counting both inpatient and outpatient cases (100% of the total). This accounted for most if not all of the “increase” in cases observed after the removal of thimerosal from Danish vaccines.



## **2)“Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data.”<sup>50</sup>**

**Authors:** Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB.

**Publication & Date:** *Pediatrics*, September, 2003

**Online at:** <http://pediatrics.aappublications.org/cgi/content/full/112/3/604>

**Details:** As in Stehr-Green, the authors looked into “whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism. This study also relied on data from the Danish Psychiatric Central Research Register on all psychiatric inpatient admissions since 1971, and all outpatient contacts in psychiatric departments in Denmark since 1995. The patient population included all children between 2 and 10 years old diagnosed with autism from 1971-2000.

**Results:** A total of 956 children were diagnosed with autism during the period. “There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990,” the authors wrote. But 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”

**Authors’ Conclusions:** Because the reported rate of autism continued to rise after the removal of thimerosal from vaccines in Denmark, the authors said, “Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism.”

### **CRITIQUES OF THE STUDY**

■ **The Same Danish Database** - Critics stated the obvious: This study was little more than a second version of the Danish section included in the Stehr-Green paper, which was published one week earlier. The main flaw in that study, of course, was the major change in the Danish registry – from including inpatient only cases, to including both inpatient *and* outpatient cases.

■ **Repeating the Swedish Mistake in Denmark** - In order to address the issue of adding outpatient cases in 1995, Madsen et al. went back and looked at inpatient cases *only*. Among this small minority of cases, they reported “the same trend with an increase in the incidence rates from 1990 until the end of the study period.” The authors failed to provide these data in their study. And the sampling was essentially identical to the Swedish analysis, in which the IOM committee (in addition to the authors) conceded that the apparent increase in autism incidence could be due to “changes in diagnostic criteria and increasing awareness of autism and related disorders.”

■ **Weakness of Ecological Studies** – This was another ecological analysis which, as the Director of the CDC, Dr. Julie Gerberding, wrote to Congress: the contributions of such studies toward establishing causality are “limited.”

■ **A Very Low Autism Rate** - Even if autism rates were shown to actually be increasing in Denmark, they were remarkably low both before *and* after thimerosal was removed. According to the Madsen study, Denmark’s prevalence rate was a tiny 1-per-10,000 - one of the lowest rates ever reported - before thimerosal’s removal. By 1999 (with the addition of outpatient cases) the rate “rose” to 4-6 per 10,000 - still very low - comparable to US rates *before* thimerosal exposures in that country tripled, around 1990. The rate was also at least *ten times lower* than the estimated 2000 US rate, 60-per-10,000.

■ **Undisclosed Conflicts of Interest** - SafeMinds and others criticized the inherent conflicts of interest among some of the study authors. Two of them worked for the Statens Serum Institut, a Danish manufacturer of thimerosal containing vaccines. According to its mission statement, “Statens Serum Institut is a public enterprise operating as a market-oriented production and service enterprise. In 2002, more than 80% of SSI profits came from vaccines.” Still, this conflict was not disclosed by *Pediatrics*.

## WHAT AN INTERNATIONAL TEAM OF SCIENTISTS SAID

In 2005, Joachim Mutter of the Institute for Environmental Medicine and Hospital Epidemiology, in Freiburg, Germany and colleagues in the UK and US published a paper in *Neuroendocrinology Letters* that included a serious indictment of the study. It echoed many of the same points made by SafeMinds and others, namely:<sup>51</sup>

- Autism counts were based on hospitalized, inpatient records in the first cohort and then changed in the middle of the study period (1995) to include outpatient records. Therefore, the purported increases after 1994 may be explained by the additional recruitment of an existing autism population that did not require hospitalization.
- After 1992, the register added in patients from a large Copenhagen clinic, which accounted for 20% of the caseload in Denmark. The patients from this clinic were excluded prior to 1992.
- The diagnostic category changed after 1993 from “psychosis proto-infantilis” of ICD-8 (code 299) to “childhood autism” of ICD-10. Another paper using the same inpatient register reports that the psychosis proto-infantilis category includes inpatient cases that do not fulfill the criteria for autism.
- Many of the children were between 7–9 years old, and most were over 4 years old, when recorded. But the onset of autism must occur, by definition in the diagnostic criteria, before three years of age. The most widely used approach to assessing autism trends is to use year of birth as the “incidence time” and to assess trends in autism rates

based on birth year of the study population rather than time at diagnosis or some other measure of incidence.

- Another recent study performed by Madsen et al. reported Danish autism rates of 6 per 10,000 for children born in the 1990s.<sup>52</sup> These Danish rates are very low in the 1990s compared to the United States. Madsen et al. also report inpatient rates for the pre-1993 “psychosis proto-infantilis” at well below 1 per 10,000. This low rate would contradict the single published survey of autism rates from Denmark, which indicated an autism rate of over 4 per 10,000 as far back as the 1950s.

- Additional confounders were present in the U.S. with high prevalence of autism that were not present in Denmark: Between 1970–92, the only childhood vaccine given in Denmark until 5 months of age was the monovalent pertussis vaccine. In the United States, children were exposed to multiple doses of diphtheria, pertussis, tetanus, polio, hepatitis B and haemophilus influenza B (Hib) vaccines before five months of age in the 1990s.

### **WHAT THE MEDIA SAID:**

The mainstream media portrayed the Madsen study as definitive. *The New York Times* declared: “Study Casts Doubt on Theory of Vaccines' Link to Autism” and quoted the CDC’s Dr. Robert Davis as saying the evidence was “clear-cut: If you remove cars from highways, you’ll see a marked decrease in auto-related deaths. If thimerosal was a strong driver of autism rates, and you remove it from vaccines, you should have seen some sort of decline — and they didn’t.”<sup>53</sup>

*The Times* also quoted Dr. William Schaffner, Chairman of Preventive Medicine at Vanderbilt University in Nashville, as claiming that the study added to “the whole mosaic of studies that have addressed this. Each is imperfect, but they all add up to this theme: thimerosal is not the culprit.”

The paper included a SafeMinds statement asserting that the researchers “artificially boosted the number of cases by adding outpatients and those at a large Copenhagen clinic to earlier inpatient figures.” It also reported that two authors worked for a Danish vaccine maker, “suggesting a conflict of interest.”

### **WHAT THE AUTHORS SAID:**

- **Outpatients “May Exaggerate Incidence”** - The authors conceded that, “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.”

- **Greater Awareness, New Diagnostics Can Boost Numbers** - The reported increase in autism in Denmark “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.”

■ **Exposure Levels Were Lower Than US** - Echoing criticism that the Danish data are not comparable to other countries, such as the US where mercury exposures were greater, the authors wrote: “Our data cannot, of course, exclude the possibility that thimerosal at doses larger than used in Denmark may lead to neurodevelopmental damage.”

#### **WHAT THE IOM REVIEW SAID:**

■ **Limited Contribution** - Adding additional outpatient cases into the Danish register was noted as a potential problem. “A reanalysis was conducted, limiting itself to inpatient data only, and the authors found similar trends in autism rates, although the data were not shown,” the IOM wrote. “However, despite the reanalysis the authors stated that autism incidence after 1995 may have been exaggerated due to the change in including outpatient cases into the Danish Psychiatric Central Register. This limits the study’s contribution to causality.”

**SUMMARY:** This study is perhaps the least informative of all the thimerosal studies. The shifting definition of cases and limitation, at any point, of only autism cases that were admitted to hospitals make this analysis thoroughly unreliable from the outset.

### **3)“Association between thimerosal-containing vaccine and autism”<sup>54</sup>**

**Authors:** Hviid A, Stellfeld M, Wohlfahrt J, Melbye M.

**Publication & Date:** *Journal of the American Medical Association*, October 1, 2003

**Online at:** <http://jama.ama-assn.org/cgi/content/full/290/13/1763>

**Details:** The authors conducted a population-based cohort study of all 467,450 children born in Denmark from January 1, 1990, until December 31, 1996. They compared those children who received a thimerosal- containing vaccine with children who were given a thimerosal-free version of the same vaccine.

**Results:** During “2,986,654 person-years,” the investigators identified 440 cases of autism and 787 cases of other autistic-spectrum disorders. “The risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thimerosal-containing vaccine and children vaccinated with thimerosal-free vaccine,” they wrote. “Furthermore, we found no evidence of a dose-response association,” an increase in the relative risk for every 25 micrograms of mercury exposure.

**Authors’ Conclusions:** “The results do not support a causal relationship between childhood vaccination with thimerosal-containing vaccines and development of autistic-spectrum disorders.”

#### **CRITIQUES OF THE STUDY**

■ **Mercury Cannot Be “Protective”** - The data in this study show that mercury is *beneficial* to infant children. Those in the thimerosal group had a relative risk of 0.85 for autism, compared with the mercury free group, suggesting a substantial (though not significant) protective effect for thimerosal. This finding is suspicious, and runs counter to all knowledge, science and common sense. More to the point, the outcome suggests the presence of unexamined or unreported bias in the study design and data management that suggest the researchers were prejudiced in a way that makes them unreliable investigators.

■ **Older Children’s Records Missing** - SafeMinds identified a flaw that could well have produced a significant loss of autism case records from the Danish register, rendering the Hviid et al. findings invalid. “The registry allows 10-25% of diagnosed autism cases to be lost from its records each year,” the group wrote in a letter to JAMA.<sup>55</sup> “The effect of this loss is such that the records will disappear from older age groups to a much greater degree than from younger age groups in any given registry year.” Older children were underrepresented in the cohort, even though they were the ones who received thimerosal-containing vaccines before 1992.

■ **Reanalysis Finds More Autism in Exposed Children** – In the same letter to JAMA, SafeMinds reanalyzed the Denmark data using an alternative method to avoid the “record

removal bias.” Instead, they looked at same-age children – 5-to-9 year olds - but from two different registry years: 1992, when all of the children received thimerosal-containing pertussis vaccines; and 2002, when none of the children received thimerosal. “After adjusting for the lack of outpatient records in the 1992 registry, the analysis found a 2.3 times higher number of autism cases among the 1992 thimerosal-exposed group relative to the 2002 non-exposed group,” SafeMinds said.

■ **No Tracking of Birth Cohorts** - The researchers failed to classify autism cases by birth year. There is often a gap between the number of children diagnosed with autism from any given birth cohort and the number of autism cases reported in any given calendar year. Analyzing the data according to birth cohort would have painted a far more accurate picture, because it would have reduced or eliminated the gap between diagnoses of ASD and reporting of cases.

■ **Undisclosed Conflict of Interest** - “In the Hviid study in JAMA we can clearly see how the data was misinterpreted so a conclusion could be drawn to clear thimerosal from any role in autism,” a SafeMinds statement said. “This misinterpretation is not surprising, given the authors’ employment at *Statens Serum Institut*, a conflict of interest that should have been disclosed.”

## **WHAT THE AUTHORS SAID**

The authors wrote that a “possible weakness” of their paper was that “the date of diagnosis used as the incidence date may differ significantly from the ‘onset of symptoms’ date.” Diagnosis autism is often “a lengthy process,” they wrote, and this is “reflected in the mean ages of diagnoses in this study (4.7 years for autism and 6.0 years for other autistic-spectrum disorders).” Such a limitation, however, “is more likely to be a problem in an incidence study than in a risk factor study.”

## **WHAT THE IOM SAID**

Although the committee considered the study as having “strong internal validity” it also identified various limitations, “including its time-series design,” (as pointed out by SafeMinds), and the “generalizability of the study’s findings to the U.S. situation, especially with regard to the different dosing schedule used in Denmark and the relative genetic homogeneity of the Danish population.”

**SUMMARY:** This study was marked by missing records, a failure to track birth cohorts, and undisclosed conflicts of interest. Reanalysis of the data actually showed an increased risk of ASD following thimerosal exposure. It also concluded that mercury had a protective effect on the neurodevelopment of children, which flies in the face of all logic and all previous studies of mercury and children.

#### **4) “Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases.”<sup>56</sup>**

**Authors:** [Verstraeten T](#), [Davis RL](#), [DeStefano F](#), [Lieu TA](#), Rhodes PH, [Black SB](#), [Shinefield H](#), [Chen RT](#); [Vaccine Safety Datalink Team](#).

**Publication & Date:** *Pediatrics*, November, 2003

**Online at:** <http://www.ncbi.nlm.nih.gov/pubmed/12880876>

**Details** – This study, conducted by investigators at the CDC using the Vaccine Safety Datalink (VSD) of computerized HMO databases was a two-part “retrospective cohort study.” The first phase looked at potential associations between neurodevelopmental disorders (NDDs) - including autism, ADD, speech and language delay and tics - and thimerosal among 124,170 US children born from 1992 to 1999 at one of two HMOs (A and B).

Because Phase I failed to find a consistent, statistically significant “signal” for autism or ADD, these disorders were excluded as study endpoints in Phase II. In that phase, the most common disorders associated with exposure in phase I (tics, speech delay and ADHD) were assessed among 16,717 children born from 1991 to 1997 in a third HMO (C). Relative risks for neurodevelopmental disorders were calculated for each 12.5 microgram increase of estimated thimerosal exposure in the first, third, and seventh months of life.

**Results:** In phase I at HMO A, exposure at 3 months of age was associated with an increased risk of tics.” The relative risk for tics was 1.89, meaning exposed children were nearly *twice* as likely to develop the disorder. At HMO B, there was an increased risk of language delay for exposure at 3 months (RR: 1.13) and 7 months (RR: 1.07). However, in Phase II at HMO C, “no significant associations were found,” and “In no analyses were significant increased risks found for autism or attention-deficit disorder.”

**Authors Conclusions:** “No consistent significant associations were found between TCVs and neurodevelopmental outcomes. Conflicting results were found at different HMOs for certain outcomes. For resolving the conflicting findings, studies with uniform neurodevelopmental assessments of children with a range of cumulative thimerosal exposures are needed.”

#### **A “SIGNAL” DISAPPEARS ACROSS FIVE GENERATIONS OF STUDY**

Critics of the Verstraeten paper question the process under which the data were managed across at least five different generations of analysis that lasted more than four years before the official version was published in *Pediatrics*. They charge that the data were put through a rather torturous process of statistical manipulation designed to get the results so badly desired by CDC: Namely, no association between thimerosal and negative outcomes.

Whether done intentionally or not, the various generations of analysis clearly show how an extremely strong “signal” between thimerosal and autism, ADD and other NDDs in the first generation was reduced to almost nothing in the fifth and final published version.

It is important to note that the first four analyses would *never* have come to light without documents obtained by SafeMinds through the FOIA. The group’s FOIA efforts likewise yielded unpublished minutes from a secret, two-day conference held in June 2000 near CDC headquarters outside Atlanta, known as the Simpsonwood Meeting. It is clear from the transcript that many industry and public health experts at Simpsonwood were alarmed by the possible harm being caused by thimerosal – but even more worried about the possible damage that any bad publicity would have on the national and global vaccine programs. Participants voted to keep the meeting secret, and it remained so for two years, when the minutes were delivered to SafeMinds. (See Below).

It is also important to note that Verstraeten himself presented results from some of the earlier VSD analyses – in which the thimerosal signal was still quite significant - to the CDC’s Advisory Committee on Immunization Practices Institute (ACIP) in 2000 and to the Institute of Medicine in 2001 without dismissing the data as being “preliminary” and therefore unreliable (also discussed below)

#### **FIRST ANALYSIS – December, 1999 -- Autism Relative Risk = 7.62**

In the very first run of the VSD data on thimerosal, lead author Thomas Verstraeten divided all of the children in HMO A and B into four groups: Those who had received zero micrograms of mercury in vaccines by one month of age, those who had received 12.5mcg, those who received 25mcg, and those exposed to more than 25mcg by one month of age.

The results were astonishing. The children exposed to more than 25mcg had extremely elevated relative risks for:

- ADHD: 11.35 times more likely
- Autism: 7.62 times more likely
- ADD: 6.38
- Tics: 5.65
- Speech and Language Delay: 2.08

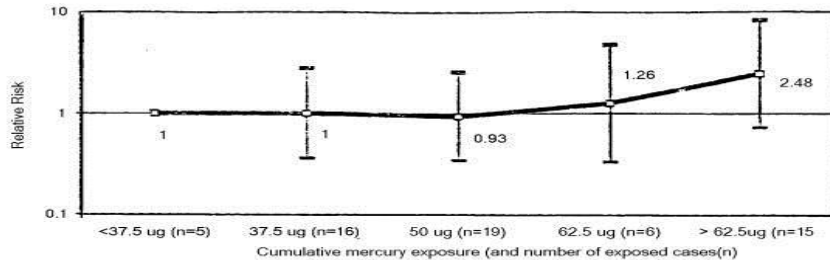
#### **SECOND ANALYSIS – February, 2000 -- Autism Relative Risk = 2.48**

Within two months, Verstraeten had reanalyzed the data, incorporating methodological changes suggested by colleagues at the CDC. In the second version, completed in February 2000, the estimated relative risk for autism had fallen considerably – though it was still worryingly high. Children in the two HMOs exposed to the most mercury (62.5mcg) at three months of age were almost two and half times more likely to develop autism (RR=2.48). This calculation was just short of statistical significance because the



low end of the margin of error fell slightly below the risk of 1.0. It's worth noting that Verstraeten excluded children who had been treated with hepatitis B immune globulins "as these were more likely to have high exposures and high outcomes." Most formulations of immune globulins were preserved with thimerosal at that time. These infants were among the most heavily exposed patients and also had dramatically higher rates of autism and other disorders, and yet they were excluded from the analysis at this stage.

**Relative risk of Autism from thimerosal exposure at 3 months of age:**



**SOURCE: Internal CDC report, February 2000 – Obtained through the Freedom of Information Act (FOIA).**

Verstraeten was nonetheless alarmed. On December 17, 1999 he sent an email to colleagues Robert Davis and Frank DeStefano under the subject line "It just won't go away," by which one presumes he meant the association between thimerosal and NDDs. "Some of the relative risks increase over the categories, and I haven't yet found an alternative explanation," he said. "Please let me know if you can think of one."

In this second analysis, Verstraeten, Davis and DeStefano candidly wrote that they had associated "increasing risks of neurological developmental disorders with increasing cumulative exposure to thimerosal." They also found "similar increases" for the risk of developmental speech disorder, autism, stuttering and attention deficit disorder, though these increases were not statistically significant. "We can state that this analysis does not rule out that receipt of thimerosal containing vaccine in children under three months of age may be related to an increased risk of neurological developmental disorders."

**THIRD ANALYSIS – June, 2000 -- Autism Relative Risk = 1.69**

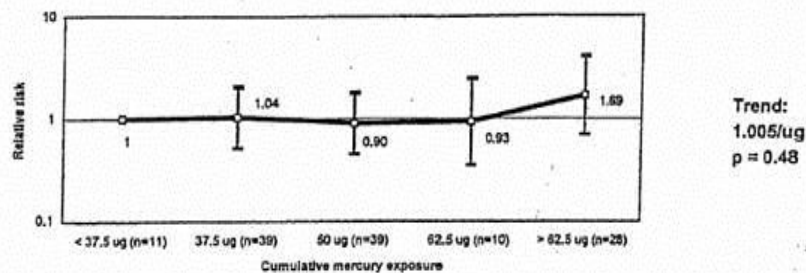
On March 9, 2000, Verstraeten sent another email, obtained through FOIA, about his work on the third generation of analyses. He wrote that the risk of developmental delay began to drop among children who missed their first thimerosal-containing HiB and DTP shots before three months of age. This confirmed his "hypothesis" that "What matters is not getting it before the third month, after which the implications gradually diminish."

Verstraeten also looked at exposure rates and outcomes among 10 premature infants and found that those exposed to 200mcg mercury were five times more likely to have an NDD than preemies exposed to 100mcg. "These findings are very extreme and warrant closer examination," he wrote.

By this time, Verstraeten et al. were preparing a third analysis of the VSD data, incorporating even more changes (i.e. entry criteria, stratification of population groups, etc) to their methodology. Critics say these changes were made deliberately to eliminate the “signal” that would “not go away” (discussed below) while CDC officials have insisted they were just trying to get the “cleanest” and most reliable data possible.

In June, 2000, Verstraeten presented the third analyses at a meeting of the CDC’s Advisory Counsel on Immunization Practices (ACIP) and at the Simpsonwood conference. This time, the relative risk for autism among children given more than 62.5 mcg by three months of age had fallen - from 2.48 to 1.69:

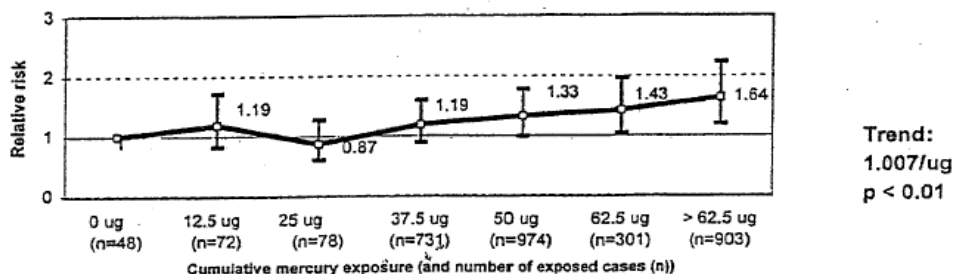
Graph 4: Relative risk + 95 % CI of Autism after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



This still-elevated autism finding was not considered statistically significant because the margin of error dipped below a relative risk of 1.0. But the team did find “statistically significant associations between thimerosal and neurodevelopmental disorders” other than autism. These included:

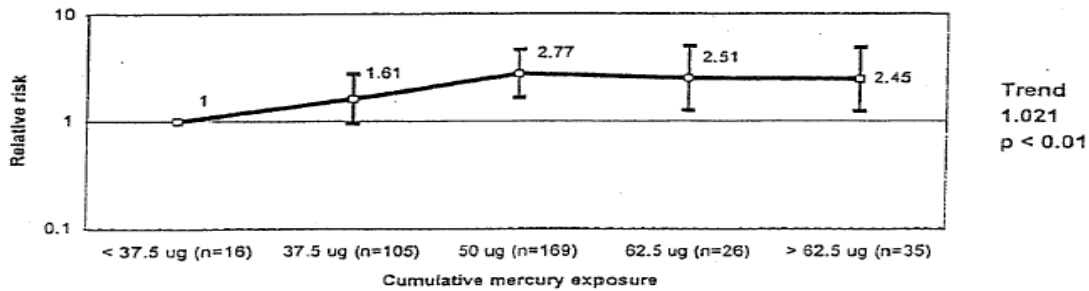
**Relative Risk for All NDDs Combined:** The RR for this umbrella category of outcomes among children exposed to 62.5mcg at three months was 1.64, meaning these children were 64% more likely to have *any* NDD than children exposed to 0mcg. The risk was considered statistically significant because the margin of error remained above 1.0. And increased risk was completely linear and dose-dependent: It increased by 0.7% for every microgram of mercury exposure:

Graph 2: Relative risk + 95 % CI of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



**Relative Risk for Developmental Language Disorder:** Statistically significant increased risks for language disorder were found at 3 months (2.1% per mcg). The RR for children receiving 50mcg mercury or more by 3 months of age was especially high. Children who received 62.5mcg had a relative risk of 2.10 compared with children who received 12.5 mcg.

Graph 12: Relative risk + 95 % CI of Developmental language disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



**Relative Risk for Attention Deficit Disorder:** There was a statistically significant, dose-dependent response at six months of age of 0.6% for each microgram of exposure. At 62.5mcg, the RR was 1:30, or 30% more likely to develop ADD.

**Other Elevated risks:** Increased risks per mcg of exposure were found for:

**Speech delay:** 1 month (RR: 1.011), 3 months (RR:1.008), 6 months (RR:1.002)

**Unspecified Delays:** 2 months (RR: 1.005), and 3 months (RR:1.007)

**Tics: 3 months:** (RR: 1.021)

“Some of these are borderline statistically significant,” Verstraeten told the ACIP meeting. “Some of them are highly statistically significant. What these estimates suggest is that there seems to be an increasing trend, an increasing risk for any of these neurological developmental outcomes, with increasing thimerosal exposure.”

## THE SIMPSONWOOD CONFERENCE – June 2000

The same month as the ACIP meeting – June, 2000 - the CDC convened an invitation-only conference at a retreat outside Atlanta called Simpsonwood, where dozens of public health officials, physicians, scientists, and industry executives gathered for a two-day, supposedly off-the-record discussion of the Verstraeten findings. The meeting was not announced to the public, and the transcript was not meant for public consumption. It was, however, included in a FOIA request packet that was delivered to SafeMinds. Members of the public were patently excluded at Simpsonwood, and industry representatives outnumbered panel members.

The task at hand was to review the VSD analysis and determine if a “signal” between TCVs and developmental disorders was there. Participants were also asked for ideas on how to proceed in the ongoing investigation, which was in its first year of what would become four years of analysis and reanalysis. Among the revelations:<sup>57</sup>

- **Troubling data** - Many attendees knew they had a problem. “What if the lawyers get hold of this?” asked one. “There’s not a scientist in the world who can refute these findings.”
- **Deference to industry** - It is clear that the CDC would not recall any mercury containing vaccines, regardless of the risks, out of concern for the financial interests of the vaccine industry. “CDC is not in favor of expressing a preference for a particular vaccine (i.e. thimerosal-free) for fear of alienating the other manufacturers and disrupting a free market economy,” one participant wrote to colleagues after the meeting.
- **Dr. Paul Stehr-Green**, an associate professor of epidemiology at the University of Washington and lead author of the Danish-Swedish thimerosal study, summarized the meeting in a memo obtained through FOIA. He wrote that, despite a prolonged “re-analyses,” the data still showed a “slight tendency for groups with higher exposure to thimerosal-containing vaccines to have higher rates of the same neurobehavioral outcomes.” But, he insisted, the level and consistency of statistical significance of these findings was “unimpressive.” The results did not “offer adequate evidence to support or refute the existence of causal relationship.”
- **Dr. Philip Rhodes** (a CDC statistician) spoke of a certain way that researchers could suppress the signal through changing the exclusion criteria: Restore thousands of children with congenital disorders who were excluded from the study, “which would serve to add ‘noise’ that could obscure the signal. All those kids that Tom (Verstraeten) has excluded, I have thrown them in. I think there is a clear argument that is going too far, but that further brings things down,” Rhodes said. “So you can push, I can pull. But there has been substantial movement from this very highly significant result, down to a fairly marginal result.”

Eventually, those previously excluded children with congenital disorders would indeed be added back into the patient population under study.

- **Dr. Thomas Verstraeten** discussed many of the study’s flaws, including the large number of young children. “One thing that is for sure, there is certainly an under-ascertainment of all of these cases,” he said. “Some children are just not old enough to be diagnosed. So the crude incidence rates are probably much lower than what you would expect, because the cohort is still very young.” As for the most common disorder found, speech delay, Verstraeten said the trend had been “highly statistically significant.” He added that the hypothesis was “biologically plausible.”

Verstraeten was very clear on one central point, however. Despite the changes in methodology and stratification of the data, the signal between thimerosal and NDDs

simply would not vanish. “You can look at this data and turn it around,” he said, “and look at this, and add this stratum, and I can come up with very high risks. And I can come up with very low risks, depending on how you turn everything around. You can make it go away for some and then it comes back for others,” he concluded. “So the bottom line is, okay, our signal will simply not just go away.”

- **Dr. William Weil**, who represented the American Academy of Pediatrics, lectured his colleagues for believing that the signal was weak and not significant:

The number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant. The increased incidence of neurobehavioral problems in children in the past few decades is probably real. Like many repeated acute exposures, if you consider a dose of 25 mcg on one day, then you are above threshold. And then you do that over and over to the same neurons. It is conceivable that the more mercury you get, the more effect you are going to get. The brain and central nervous system are not fully developed at birth. The earlier you work with the central nervous system, the more likely you are to run into a sensitive period for one of these effects. It changes enormously the potential for toxicity. There’s a host of neurodevelopmental data that would suggest that we’ve got a serious problem. To think there isn’t some possible problem here is unreal. The number of kids getting help in special education is growing nationally and state by state at a rate we have not seen before. The rise in the frequency of neurobehavioral disorders is much too graphic. We don’t see that kind of genetic change in 30 years.

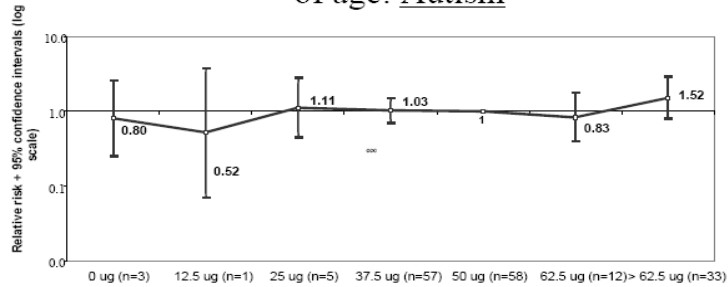
- After the meeting, Verstraeten sent an email to colleagues complaining of the indifferent stance that most of the participants took toward the thimerosal signal that “won’t go away.” Their attitude seemed to be that, “if nothing is happening in these studies, then nothing should be feared of thimerosal,” he wrote. “I do not wish to be the advocate of the anti-vaccine lobby and sound like being convinced that thimerosal is or was harmful, but at least I feel we should use sound scientific argumentation and not let our standards be dictated by our desire to disprove and unpleasant theory.”

#### **FOURTH ANALYSIS – July, 2001 -- Autism Relative Risk = 1.58**

In this fourth analysis, presented at the July 2001 meeting of the IOM’s Immunization Safety Review Committee, the VSD team had decided to divide HMO A and B and examine their data separately.

But HMO B, with some 15,000 patients studied, was considerably smaller than HMO A, which had 115,000 patients. After breaking them into two subpopulations, they found that data from the smaller HMO were no longer statistically significant. The smaller HMO simply lacked the “statistical power” of the larger HMO and therefore, results from the two HMOs were no longer “consistent.” The same was true for speech and language delays.

Relative risk associated with exposure at 3 months  
of age: Autism



Note: provisional results - may be subject to change



Even so, for some of the estimates, “we found high statistical significance,” Verstraeten told the IOM. “Some of these associations are biologically plausible, and for some, we saw a dose response.”

By now, the team had also completed Phase II of the study, which was to compare results from HMOs A and B with a third, independent HMO, in this case, Harvard Pilgrim of Massachusetts. And though Phase I had found “several significant associations between thimerosal and neurodevelopmental disorders,” Verstraeten said, “in an analysis in a smaller and independent data set, we could not confirm those associations for speech or language delay and ADHD.” And given the lack of statistically significant risk for autism, the team had stopped looking at that outcome altogether in the Harvard Pilgrim data.

The reliance on HMO C to discount the entire study was criticized by Neal Halsey (title here) “Some people who have seen the third HMO, which is Harvard Pilgrim, have said there is no effect there, therefore that disproves the hypothesis,” he testified at IOM. “Well, that is really not true. I don't know what the real power is of that study to say that there really isn't an effect there. Power is a very important factor in studies that don't show an effect.”

The data were inconclusive, but “still suggestive of an effect from thimerosal,” he said.

**FINAL ANALYSIS – November, 2003 -- Autism Relative Risk = N/A**

By the time the study was published in 2003, the authors found just one increased risk for tics in phase I: At HMO A, exposure at 3 months the relative risk was 1.89. At HMO B, B, there was an increased risk of language delay for exposure at 3 months (RR: 1.13) and 7 months (RR: 1.07). But in Phase II at HMO C, “no significant associations were found.” And “in no analyses were significant increased risks found for autism or attention-deficit disorder.”

This was untrue. In the first analysis, there were significant increased risks for autism and ADD, and in the second analysis, there was a significant increased risk for ADD.

## **CRITIQUES OF THE STUDY**

How did the relative risk for autism tumble from 11.35 to null? The four-year, five-generation analysis has been examined closely by many critics, both inside the autism community and among respected scientists, physicians and members of Congress. The many methodological flaws they have identified include:

■ **Inclusion of Young Children** - Researchers included young children, from 0-3 years old, even though the average age of an autism diagnosis was 4.4 years. A diagnosis in the first years of life was rare, so including these children would tend to drive down the overall relative risk. Because they were not yet diagnosed, all of them would have been misclassified under the normal group. But the CDC assumed that autism is diagnosed as frequently in 1-year-olds as five-year-olds.

■ **No Autism Diagnoses Among Youngest Children** - Among the youngest children, who made up 40% percent of all kids in the study, not a single case of autism was reported, which means that 40% of the sample was misclassified.

■ **Underreporting of Autism Cases** - The researchers identified relatively few kids with autism compared to what one would expect to find in the general population. In California at the time, the autism rate (excluding PDD and Aspergers) was around 50-100 per 10,000 children. But the average rate at the two California HMOs was just 11.5 per 10,000. Had they missed, or somehow eliminated four out of five cases? What else could explain this dramatic under-ascertainment? This undercount clearly also means that these cases were misclassified.

■ **Exclusion of ASD cases other than “autism”** - The researchers did not look for outcomes like PDD-NOS and Asperger’s Syndromes, even though they are autism spectrum disorders. This meant that higher-functioning children were not included in the risk ratios. ■ **Stratification of Data** – The authors not only separated HMO A and B to find that data from the smaller HMO alone lost statistical power, they even broke up the larger HMO into subgroups comprised of individual clinics in the network. This “stratification” helped eliminate any consistent statistically significant risk of ADHD or speech disorders that were found within the larger HMO as a whole. Smaller population subgroups have less “statistical power,” and increase the possibility that statistical significance will not be attained.

■ **Elimination of the combined “NDD” Outcome** - By breaking this generalized umbrella outcome into individual categories like ADHD, speech delay and tics, the relative risks and statistical significance of most outcomes were reduced or eliminated. Again, the smaller the stratified subgroup, the greater the chance of reducing statistical power and thus statistical significance.

■ **Elimination of cases diagnosed outside the HMOs** – The authors chose to include only those cases confirmed by a behavioral specialist. But if that specialist was outside the HMO, the diagnosis was not counted. This provided the opportunity to “cherry pick” cases out of the original data set. Among the ADD/ADHD cases, 60% were eliminated because they were not made by an in-network specialist. For speech and language delay, 50% were excluded and for autism, 20% were eliminated.

■ **Higher risk with increased vaccination** - Generally speaking, among the three HMOs studied, the higher the vaccination rate, the greater the risk of adverse outcomes. During the third generation of analysis, for example, HMO C had the highest full vaccination rate, at 65%, and also the highest speech delay rate. Meanwhile, at HMO A, the fully vaccinated rate was 60%, or four times greater than compliance at HMO B (15%), while the rate of all NDDs at HMO A was 5.7%, four times greater than the 1.3% rate found at HMO B.

	HMO A	HMO B	HMO C
Full vaccination rate	60%	15%	65%
NDD rate	5.7%	1.3%	n/a
Speech delay rate	3.9%	2.6%	4.5%

■ **Problems at Harvard Pilgrim** - There were questionable record keeping practices at Harvard Pilgrim (HMO C), and Massachusetts had been forced to take over after it declared bankruptcy. Even worse, the HMO used different diagnostic codes than the other two HMOs in Phase I. It wasn’t surprising that the Harvard Pilgrim data was inconsistent. Also, the study population at Harvard Pilgrim was significantly smaller (15,000 kids). The smaller the population studied, the greater the margin of error, which lowers the study’s “statistical power” and weakens the signal for outcomes.

■ **Undeclared conflict of interest.** After Verstraeten began work at GlaxoSmithKline, “the data, sampling and methodology of the study were altered, so that results would point to enough inconsistencies to cast doubt that mercury in vaccines causes autism,” critics alleged. Verstraeten had not been named as a GSK employee in the study and was misidentified as an employee of the CDC. It must be noted that GSK made thimerosal-containing vaccines included in the study, such as Hepatitis B and DTaP vaccines.

■ **Unavailability of data** - “The current practice of restricting access to the database to a limited group of possibly biased individuals is not acceptable,” SafeMinds declared. Their statement added that the *Pediatrics* report “cannot be accepted as final.” CDC rules had made the approval process long and arduous. Those who did gain access (the Geiers) could only “utilize a limited portion of the VSD data set, and their examination of the data is subject to constant monitoring by CDC staff.”

## WHAT THE MEDIA SAID



*Associated Press* – Co-author Frank DeStefano “acknowledged that the early results suggested stronger links with some disorders, though not autism, but denied that there had been pressure or a cover-up. He said the final data reflect a more thorough recent analysis. Verstraeten, who left the CDC in July 2001, did not respond to an email request seeking a response, and company spokeswoman Nancy Pekarek said he did not wish to discuss the results, but provided a statement in which Verstraeten said that ‘since leaving the CDC he was only an adviser as the study was finalized and prepared for publication.’”<sup>58</sup>

## **WHAT THE CDC SAID**

CDC spokesman Von Roebuck told *Insight on the News* magazine that, “We pretty much looked into that [the manipulation of data] in the sense of how the information was presented, and we do stand behind it.” As for Verstraeten’s undisclosed employment at vaccine maker GSK, he said. “The one thing that we would want to happen differently is that would have been known before. But the work that Dr. Verstraeten did was for the CDC at the time the work was produced – the work that he did for the study was done when he worked for the CDC.”

## **WHAT LEADING VACCINE EXPERTS SAID**

Dr. Neal Halsey, the national vaccine expert, along with colleagues Daniel A. Salmon and Lawrence H. Moulton, published a letter in the journal *Pediatrics* calling for further analysis of the data which included the following critiques:<sup>59</sup>

- **Changing Criteria** - By eliminating the combined umbrella outcome of NDDs, and dividing it into separate diagnoses, the authors “may have substantially reduced the power to find important relationships,” Halsey et al. said, adding that the later entry criteria “appear to have been more lax” than in a previous version.
- **Excluding Diagnoses** - The requirement that diagnoses be made by an in-network specialist was also questioned. “Were diagnoses that were not made by a specialist excluded from analyses?” they asked, noting that primary care doctors are quite “capable of diagnosing ADD without input from a sub-specialist.”
- **Unequal Population Sizes** – Halsey et al. also criticized the comparing of data from a large HMO with two much smaller ones.

## **WHAT VERSTRAETEN SAID**

In a letter published in the April, 2004 issue of *Pediatrics*, Verstraeten wrote that, while his team had found a positive association between thimerosal and certain outcomes in Phase I, these findings could not be replicated in the second phase.<sup>60</sup>

But this in no way disproved an association (at least for NDDs other than autism), he insisted in a declaration that is seldom, if ever quoted today. “The perception of the study changed from a positive to a neutral study,” he said. “Surprisingly, however, the study is being interpreted now as negative by many, including the anti-vaccine lobbyists. The article does not state that we found evidence against an association, as a negative study would. It does state, on the contrary, that additional study is recommended, which is the conclusion to which a neutral study must come.”

“Did the CDC water down the original results?” Verstraeten asked, and then answered: “It did not.” Despite the fact that vaccine safety activists were charging that a “positive” study had been manipulated into a “negative” one, the study results were *neutral*; they proved nothing for either side of the debate. Presumably, the point he was making is that a deliberately manipulated study would have yielded a negative result, and not a neutral one.

“Did the CDC purposefully select a second phase that would contradict the first phase?” Verstraeten also asked. “Certainly not. The push to urgently perform the second phase at (Harvard Pilgrim) came entirely from myself, because I felt that the first-phase results were too prone to potential biases to be the basis for important public health decisions. (It) was the only site known to myself and my coauthors that could rapidly provide sufficient data that would enable a check of the major findings of the first phase in a timely manner.

And he added this:

The bottom line is and has always been the same: an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and more study is required.

### **WHAT A SPECIAL PANEL OF THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES SAID**

On August 24, 2006, a special panel appointed by the NIEHS issued a report titled “Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink.”<sup>61</sup> Among other things, the panel was asked to “Identify the strengths and weaknesses of the VSD for evaluating the possible association between exposures to thimerosal-containing vaccines and AD/ASD”

According to the panel, “a number of gaps were identified in the information available at the meeting. These involved business and medical practices at the MCOs that might impact data quality and interpretation of study results, and more generally, the completeness and validity of exposure and diagnostic data in the VSD and the ability to link across family members.” The panel recommended that these gaps be addressed prior to consideration of further studies of ASD and thimerosal using the VSD.

The panel also “identified several areas of weakness,” the report said. “The cumulative effect of these weaknesses was judged to reduce the usefulness of the VSD for addressing the potential association between exposure to the vaccine preservative thimerosal and risk of AD/ASD.”

The weaknesses of primary importance are summarized below.

**Case ascertainment** - “Of particular interest to the panel was the large proportion, around 25%, of births excluded from the analyses in the Verstraten study. These exclusions were intended to decrease confounding. The panel noted that these children may represent a susceptible population whose removal from the analysis might have had the unintended consequence of reducing the ability to detect an effect of thimerosal. A VSD study that relies exclusively on administrative data to identify cases of ASD is subject to both false positives and missed cases. This stems in part from the original design of the data systems that support the VSD; these systems were designed for administrative rather than research purposes. For example, the administrative record created for an outpatient visit of a child with AD/ASD who is being treated for another medical condition will reflect that other condition rather than the presence of autism. Entries of this type would lead to under-ascertainment of cases.”

**Heterogeneity in business practices across and within MCOs (HMOs)** – “Eight MCOs currently participate in the VSD and each relies on data systems designed to meet the specific business requirements of the MCO. In addition to obvious differences among MCOs in enrollment size and geographic location of the populations served, many other aspects of service delivery and tracking vary (e.g., developmental screening practices and specialist referral guidelines). Differences across clinics and other service providers affiliated with an individual MCO occur as well. The panel noted that these variations within and among VSD sites would complicate interpretation of a VSD study that combined data across clinics and sites by introducing heterogeneity in the completeness and quality of case ascertainment. Moreover, membership in an MCO might be influenced by an AD/ASD diagnosis. This could occur, for example, if children presenting with problems predictive of the development of AD/ASD (e.g., speech delay) are more likely to leave a MCO-administered plan because the parents believed that another model of service delivery would be more beneficial.”

**Systematic changes over time** – “The systems for creating medical records at the VSD sites are dynamic and change frequently in response to the evolution of the individual MCO business model. The panel noted that at least some of these changes would be expected to affect the observed rate of autism and could confound a trend analysis. One such change was the transition from paper to electronic medical records. This change occurred at different times for each of the participating MCOs.”

**Estimation of mercury burden.** “Panel members expressed a concern that thimerosal dose, administered through a series of vaccinations, may provide a poor surrogate measure of the cumulative exposure of a child to organic mercurials. Exposures through

diet or other environmental sources would not be documented reliably in either the VSD administrative data or medical charts.”

**Transparency and Public Access** – “The panel recognized the perception by some members of the public and the advocacy community that previous VSD analyses have not been conducted in an open manner. The panel recommended that the AD/ASD advocacy community participate meaningfully in all aspects of any future VSD study of AD/ASD, including design, analysis and interpretation.”

**CRITIQUE BY IRVA HERTZ-PICCIOTTO, PHD, MPH, CHIEF OF THE DIVISION OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH, UNIVERSITY OF CALIFORNIA, DAVIS SCHOOL OF MEDICINE**

“The appropriateness of exclusions that amounted to nearly 25% of the birth cohort in the investigation by Verstraeten et al. (2003) was questioned in the NIEHS expert panel report, and (CDC Director) Dr. Julie Gerberding concurred that further work should be done using the VSD to address this weakness.”<sup>62</sup> The VSD study “was not the last word... things need to be looked at again, perhaps with different methodology.”<sup>63</sup>

**WHAT A LEADING CRITIC IN CONGRESS SAID**

Former Rep. Dave Weldon, MD (R-FL), who served as only one of two physician members of Congress, wrote to CDC Director Dr. Julie Gerberding about his “serious reservations about the four-year evolution and conclusions of this study.”<sup>64</sup>

“I have read various emails from Dr. Verstraeten and coauthors. I have reviewed the transcripts of a discussion at Simpsonwood. I found a disturbing pattern which merits a thorough, open, timely and independent review by researchers outside of the CDC, HHS, the vaccine industry, and others with a conflict of interest in vaccine related issues (including many in University settings who may have conflicts), he wrote.

Instead of a “good faith effort” to investigate potential harm from thimerosal, “there may have been a selective use of the data to make the associations in the earliest study disappear,” he charged. “I cannot say it was the author’s intent to eliminate the earlier findings of an association. Nonetheless, the elimination of this association is exactly what happened and the manner in which this was achieved raises speculation.” The Simpsonwood transcripts, he added, “clearly indicated how easily the authors could manipulate the data and have reasonable sounding justifications for many of their decisions.”

**WHAT THE IOM SAID**

The IOM vaccine safety committee was not troubled by the changing criteria for entry and outcomes, nor did the total disappearance of an autism signal concern them.

“The difference in preliminary results can be attributed to three major reasons,” they said:

- “Investigators updated datasets with extended follow-up periods, which allowed for additional cases to be identified.”
- “They modified exclusion criteria based on scientific input from the (2001) IOM report and CDC and VSD investigators
- “They improved adjustments for health-care-seeking behavior.
- “Other reasons cited for the differences were a modification to the time of exposure, and inclusion of additional variables in the model.

The panel added this:

The committee notes that it is commonplace for large and important studies to be reviewed along the way, with adjustments often made to improve the eventual validity of the results; thus, it finds nothing inherently troubling in the fact that the VSD study underwent this process. The committee also notes that preliminary results are often misleading and can change substantially as methods are adjusted and more cases and controls are assembled. Indeed, the fact that a conference was held to discuss preliminary findings (Simpsonwood) would typically be interpreted as an attempt by researchers and their sponsors to “get it right,” given the high level of interest in the findings.

**Under-ascertainment of cases?** The IOM panel wrote that, for HMO A, the autism rate was 1 in 635, or 15.7-per-10,000, and HMO B had 1 in 523, or 19-per-10,000). “Several concerns were raised about the possibility of misclassification of cases with autism because of the way the age of the child was handled in the analyses,” they wrote. One worry was that “some cases of autism may have been missed with shorter follow-up.” But, the data “were adjusted for month and year of birth and time of follow-up,” a “statistical-analysis technique” that “should therefore take care of this concern,” the panel said, without explaining how.

**Inclusion of younger children** – “Another related concern was that inclusion of a younger group (who are less likely to be diagnosed with autism) in the study would bias the thimerosal effect toward zero,” the panel wrote. “Adjusting for age would reduce, but not eliminate, this tendency. However, if there were an effect of thimerosal, one still would anticipate a trend of increasing effect with age. In this study, there was no such association, even in the older age groups.”

**Misdiagnosis of younger children** – “The authors attempted to address this by determining the association between thimerosal and neurodevelopmental outcomes and found no consistent significant associations,” the panel said. But it conceded this very important point, often overlooked by the media: “If there are multiple pathways leading to these disorders, it would be difficult to detect the effect of any one cause—unless it occurred with high frequency and the sample size was large—because the tendency of misclassification of outcome is to dilute measures of effect.”

## **General Limitations cited by the IOM**

- “The authors were unable to control completely for other potential confounding factors. In HMO B, the clinic that a child attended may have acted as a confounder.” In other words, inconsistencies between record keeping practices – even within the same HMO – render the data less reliable.
- “The HMO databases did not provide information on other possible confounders, such as maternal smoking, lead exposure, or fish consumption.” Total accumulated toxic exposure is probably more important than a single type of exposure from a single source (ie, mercury in vaccines). Background exposures should also be included.
- “Limitations include the study’s ability to answer whether thimerosal in vaccines causes autism because the study tests a dose-response gradient, not exposure versus non-exposure.” This study compared children who received the highest doses of thimerosal with children who received lower doses. Studying exposed versus non-exposed children might yield clearer data.
- “The small number of cases and instability of some of the risk estimates may affect the findings.” The number of autism cases found was quite low - far lower than what would be expected for such large HMOs.

**SUMMARY:** This highly controversial study is considered the most important by people who reject any link between thimerosal and ASD, yet it is fraught with severe limitations, methodological weaknesses and questionable analyses. Data collected from the HMO’s was repeatedly re-analyzed – at least five times across three years of study. During that time, entry criteria were changed, children too young to have an ASD diagnosis were added, and other questionable methods of analysis were used. The relative risk for autism fell from 11.35 to zero during that time. As for other NDDs, even the lead author wrote that this was a “neutral” study and could not be used to support or refute a link.

**5) “Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association.”<sup>65</sup>**

**Authors:** [Andrews N](#), [Miller E](#), [Grant A](#), [Stowe J](#), [Osborne V](#), [Taylor B](#).

**Publication & Date:** *Pediatrics*, September, 2004

**Online at:** <http://pediatrics.aappublications.org/cgi/content/full/114/3/584>

**Details** – This study was “designed to investigate whether there is a relationship between the amount of thimerosal that an infant receives via diphtheria-tetanus-whole-cell pertussis (DTP) or diphtheria-tetanus (DT) vaccination at a young age and subsequent neurodevelopmental disorders.” It was a retrospective cohort study of 109,863 children born in the UK from 1988 to 1997. Outcomes studied were general developmental disorders, language or speech delay, tics, attention-deficit disorder, autism, unspecified developmental delays, behavior problems, and others. “Exposure was defined according to the number of DTP/DT doses received by 3 and 4 months of age and also the cumulative age-specific DTP/DT exposure by 6 months.”

**Results:** “Only in 1 analysis for tics was there some evidence of a higher risk with increasing doses (HR: 1.50 per dose at 4 months). Statistically significant negative associations with increasing doses at 4 months were found for general developmental disorders (HR: 0.87), unspecified developmental delay (HR: 0.80) and attention-deficit disorder (HR: 0.79; 95% CI: 0.64-0.98). For the other disorders, there was no evidence of an association with thimerosal exposure.”

**Authors’ Conclusions:** “With the possible exception of tics, there was no evidence that thimerosal exposure via DTP/DT vaccines causes neurodevelopmental disorders.” For general developmental disorders, unspecified developmental delay, and ADD, there was an apparent protective effect from increasing thimerosal exposure.

## **CRITIQUES OF THE STUDY**

■ **Mercury is Not Protective** - Many observers felt that the “protective effect” of organic mercury exposure found in young children was biologically implausible. According to this study, higher thimerosal exposure at 4 months of age reduced the risk of ADD and unspecified developmental delay by at least 20 percent compared to children with lower exposures. There is no biological evidence to suggest that a known neurotoxin like ethylmercury can be beneficial to neurodevelopment.

■ **A Deceptive Study Design** – When researchers try to determine if there is a cause-and-effect relationship between two different things – in this case thimerosal exposure and autism outcomes – they make their calculations using something called a “regression analysis,” which, in its simplest form, most people know of as a “curve.” A simple regression analysis has two variables. In this case, thimerosal (the potential causative

agent) would be the “independent variable,” and autism (the potential effect of the agent) would be the “dependent variable.” It is important to note as well that this is not an analysis of exposure or not, but only the timing of vaccination. *All* of the children in this study were exposed to thimerosal

But in Andrews et al., the authors used a model that was a bit more complicated, something called a “multiple regression analysis,” which had one dependent variable (autism), and multiple independent variables, including *two* independent variables (thimerosal exposure levels, and year of birth) that were “correlated” with each other, since thimerosal exposures went up with time. This creates a well-known problem in regression known as “multicollinearity” It is illogical to include both variables unless you believe the increases over time are only due to improved awareness. If there is no logic to including a variable in a regression model, it simply doesn’t belong there. In this case, since the time variable and the vaccine exposure variable are correlated, they actually compete to explain the outcome effect. Inclusion of the time variable reduces the significance of the exposure variable. Yet the authors never explained why they included a time variable that correlates and competes with the exposure variable. Instead, the Andrews model assumes implicitly that increased autism rates are due to time trends alone.

■ **Lack of Transparency** – The authors have repeatedly declined to make their data available to others for independent verification, and they fail to state why they chose such an erroneous method that would produce multicollinearity. “It’s a flaw of the peer review process, because someone should have called them on it,” said Mark Blaxill of SafeMinds. “But Pediatrics wants the outcome they report, so no one requires them to be transparent.” The AAP and its journal *Pediatrics* receive millions of dollars a year in advertising and other funds from major pharmaceutical companies, including vaccine makers. This clear conflict of interest was never mentioned in mainstream media coverage of this subject.

■ **Potential Conflicts of Interest** – Some of the authors have ties to vaccine manufacturers and/or the national immunization program of the United Kingdom. For example, Elizabeth Miller, FRCPATH, was the architect of the UK vaccine program and has testified in court in defense of drug companies in vaccine injury lawsuits.

■ **Results Not Applicable to US** - Where infant exposures to mercury from vaccines was considerably higher.

## WHAT THE AUTHORS SAID

The authors acknowledged several limitations in their study:

■ The outcomes measured occurred “at a relatively young age” and were “more likely to be affected by confounding factors that are also associated with delayed or incomplete vaccination.”



- Another limitation was the “inability to adjust for many potential confounding factors, such as unrecorded medical conditions and socioeconomic factors.”
- “If the increased risk in the US study were attributable only to the additional thimerosal exposure after 4 months of age, then it is possible that our study may not have been able to detect the risks found in the US study.”
- Validation exercises found that 20% of the diagnoses were invalid or questionable. “This lack of specificity is a limitation of the study because it biases against finding an association.”
- As for the risk of minor transient tics, “the possibility of a true effect cannot be ruled out,” although it was more plausible that the association “is a chance effect or the result of confounding.”

### **WHAT THE IOM SAID**

The IOM panel noted the differences in mercury exposure rates in the US and UK vaccines scheduled. “With the (UK’s) 2-3-4 month schedule, children could have received a maximum of 50mcg of mercury at 3 months of age and 75mcg of mercury at 4 and 6 months of age. This amount is less than the maximum amount received by U.S. children. U.S. children could have received 75 mcg of mercury after 3 months, 125 mcg after 4 months, and 187.5 mcg after 6 months.

**What Irva Hertz-Picciotto, PhD, MPH, Chief of the Division of Environmental and Occupational Health, University of California, Davis School of Medicine, said:**

Andrews et al. (2004) examined a specific hypothesis, namely, that autism risk would be increased from early administration of thimerosal-containing vaccines, based on the number of vaccines received prior to 3 months, prior to 4 months, and the timing and number of vaccines prior to 6 months of age. The unexplained oddity that three of the nine categories of developmental disorders (general developmental disorders, attention deficit disorders, and unspecified developmental delay) were significantly reduced in those with early vaccines would suggest the possibility that confounding (acknowledged by the authors as a problem) could have resulted in a 'healthy vaccinee' effect. In other words, the healthiest babies would be those who were vaccinated at the earliest times.<sup>66</sup>

**SUMMARY:** This study used a statistical sleight of hand to make any association disappear. The authors included a time variable that competes with the exposure variable. Such a model assumes *a priori* that increased autism rates are due to time trends alone. This study also suffered from some of the most serious undisclosed conflicts of interest among all the thimerosal ASD epidemiological investigations.

## **6) “Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years”<sup>67</sup>**

**Authors:** Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, Lewis E, Eriksen E, Ray P, Marcy SM, Dunn J, Jackson LA, Lieu TA, Black S, Stewart G, Weintraub ES, Davis RL, DeStefano F; Vaccine Safety Datalink Team.

**Publication & Date:** *New England Journal of Medicine*, September 26, 2007

**Online at:** <http://content.nejm.org/cgi/content/full/357/13/1281>

**Details:** Although autism was not included in this study, it is still presented as evidence against any association between thimerosal in vaccines and certain immune-globulins given during pregnancy and adverse outcomes.

Investigators studied 1,047 children between 7 and 10 years of age enrolled in participating HMOs of the VSD database. The children were given standardized tests for 42 neuropsychological outcomes, including speech and language disorders, verbal memory, achievement, fine motor coordination, visuospatial ability, attention and executive-functioning tasks, behavior regulation, tics, and general intellectual functioning.

Attention, hyperactivity and executive functioning were based on reports from parents and teachers, while motor tics, phonic tics and stuttering evaluations combined ratings by evaluators with reports from parents and teachers.

Mercury exposure from thimerosal was determined from computerized immunization records, medical records, personal immunization records, and parent interviews. The authors “assessed the association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period (birth to 28 days), and the first 7 months of life.”

**Results:** Among the 42 outcomes studied, only a few significant associations with exposure to thimerosal were detected. These associations were “small and almost equally divided between positive and negative effects.” For example:

- Higher prenatal mercury exposure was associated with better performance on one measure of language and poorer performance on one measure of attention and executive functioning.
- Increasing levels of mercury exposure from birth to 7 months were associated with better performance on one measure of fine motor coordination and on one measure of attention and executive functioning.

■ Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination.

**Conclusions** “Our study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years.

**Critique by Mark D. Noble, PhD - Professor of Genetics and of Neurobiology and Anatomy, University of Rochester Medical Center:**<sup>68</sup>

**Poor Confirmation of Cases** – “One of the most critical problems with the studies of Andrews et al. is the very poor validation for the data that they analyzed. Validation responses were received from 162 of 166 general practices that were queried, of which it appears that each was asked about a single child. Of this group, 19% of diagnoses could not be confirmed. Of those with a confirmed diagnosis, 39% were considered to be transient problems (which is not a description that would normally be applied to autism) and the duration of the problem could not be determined for an additional 35% of cases. Thus, only 26% of the validation attempts established that problems were long-term in children with a confirmed diagnosis.”

**Low Number of Unexposed Children** – “The number of individuals reported to receive no thimerosal exposure during the first 4 months of life was very low, representing only 3.4% of infants delivered at term and 5.8% of pre-term infants.”

“The small numbers of children with behavioral differences were spread in unspecified distributions across the ten years of information, and attempts at validation provided confirmation of long-term problems in only 20.5% of cases. (This) renders analysis of the data base of Andrews and colleagues fraught with uncertainty. In the specific context of autism, any decreased representation in the zero-exposure cohort (i.e., less than a total of 3 cases identified) seems unlikely to be suitable for accurate statistical comparisons.”

**Mercury As “Neuro-protective”?:** “Claims made that increased exposure to thimerosal was associated with equal or even lower levels of hazard thus appear to be conjectural. Moreover, children also exposed to hepatitis B and/or influenza vaccinations in the first six months of life were excluded from the analysis, thus excluding those children known to have still higher levels of thimerosal exposure and further limiting the values of the comparisons conducted.”

**Critique by Mary Catherine DeSoto, PhD, and Robert T. Hitlan, PhD, Department of Psychology, University of Northern Iowa:**<sup>69</sup>

Seven of the authors had received fees from Merck, Kaiser Permanente and other pharmaceutical companies that may have or had an interest in disproving any link to thimerosal and/or mercury exposure and developmental disorders. First, it is important to be very clear that we do not believe that authors would

purposefully change their data, or consciously misstate conclusions. Not only would this be unethical, but the stakes are very high. But this does not mean there is no bias; the bias would be subtle and far less nefarious than any sort of purposeful altering of data. If a person has publicly staked his/her career on a certain position being right, it may become harder to keep a truly open mind, even when new data become available and even when the original intent was to be objective. A way this bias might manifest itself is an overstatement or slight misstatement of results. We feel that both sides have been guilty of this, and this happens when a person becomes so confident in the correctness of his/her own view that he/she no longer reviews evidence to the contrary. Unconscious bias may exist even in the best scientists

This is the sort of bias, whether conscious or unconscious, that occurs. Because some of the authors of the Thompson study have publicly aligned with opposing a mercury-autism link (by taking consulting fees), they may be unconsciously more prone to review studies that support their view, less likely to review opposing viewpoints, and may eventually become unaware of relevant research (e.g., Newland et al. 2008). By using 42 measures and finding only a small handful of effects, it is easy to say the obtained relations are chance occurrences. Then, another scholar summarizes the study and slightly changes the results based on a world view that there is no effect of thimerosal, “found no evidence of neurological problems in children exposed to mercury containing vaccines” (Offit 2007, p. 1279). Then this assessment gets quoted by those who do not bother to look carefully at the original study, and scientific advancement becomes stifled.

## **OTHER CRITIQUES OF THE STUDY**

- The response rate was extremely low. Of 3,648 children selected for recruitment only 1,107 (30.3%) were tested. Among those not responding, 1,026 could not be located, while the mothers of 959 children refused participation. 68% of those refusing cited lack of time, but 13% reported “distrust of or ambivalence toward research
- Mothers with special needs kids are usually those with the least amount of free time. With such a low response rate, the children studied were likely healthier than the general population.
- Among a population of 1,026 children, one could expect to find about 45 students on medication for ADD/ADHD. Was that the case? “There were a small number of kids” with ADD/ADHD, Dr. Thompson said, without providing a number.
- It is possible that low birth-weight kids had increased deficits, but children born below 5.5lbs were excluded from the study.
- Some children had probably received years of therapy to treat outcomes they were being tested for. An unreported number had been treated with prescription drugs, speech

therapy, psychotherapy and/or other forms of treatment. Investigators conceded that prior therapy "may have ameliorated the potential negative effects of thimerosal exposure," and "could have biased the results toward" finding nothing.

- Despite the mix of positive and negative associations, there remained a "higher likelihood" of motor and phonic tics in boys, something found in previous studies, including Verstraeten (US) and Andrews (UK).
- Boys exposed to the highest amounts of mercury by 7 months of age were 2.19 times more likely to have motor tics, and 2.44 times more likely to have phonic tics than boys in the lowest exposure rates.
- The authors failed to differentiate between "transient" tics, which go away within a year, and "chronic" tics, which can last a lifetime. Nor did they distinguish between "simple" and "complex" tics. "We did not categorize them, and some of them may have been chronic," Dr. Thompson said.
- In fact, "The replication of the (2003) findings regarding tics suggests the potential need for further studies," the authors wrote.
- There were also small but negative associations with speech-articulation in children, and lower verbal IQs among girls, which together "suggest a possible adverse association between neonatal exposure to mercury and language development," the authors said. A similar "increased risk of language delays at one HMO associated with thimerosal-containing vaccines," was found in Verstraeten's 2003 VSD study.
- It is illogical to cite an increased risk for tics (one replicated in a prior study and which may need "further study") and increased language deficits (also found in the same prior study), but still conclude that there is "no causal association" between thimerosal neuropsychological deficits.
- Sallie Bernard of SafeMinds, the only consumer representative on the study's panel of advisors, said the final conclusions were mere "conjecture." The many limitations "preclude any reasonable determination of the 'truth.' The authors' arbitrary selection of one explanation for their conclusion risks misleading the reader into thinking that the absence of a relationship has been proved."<sup>70</sup>
- Dr. Lawrence Rosen, a pediatrician who treats ASD in Tappan, NJ, said the mixed results and severe limitations "make the study kind of worthless. They are picking and choosing what they want to report. It's not a well-designed study. So either don't publish it; or do so with all sorts of explanations. You can't have it both ways. This study doesn't answer any questions. It makes things even muddier."<sup>71</sup>
- Extremely few children received no thimerosal: the investigators largely compared medium-to-high exposures to low exposures, instead of zero exposure.

## **DEFENSE OF THE STUDY**

■ Dr. Ted Schettler, science director of the Science and Environmental Health Network, said there were “only a few significant associations, small and equally divided. When looking at multiple outcomes, some favorable and some unfavorable, it’s very common for authors to conclude that chance variability is the reason.”<sup>72</sup>

■ Dr. Thompson said tics were “likely to be transient,” and not of clinical importance. They were also detected by trained experts, not parents, meaning they were “probably” not severe enough for parents to notice. “And given that kids that age (7-10) have the greatest degree of transient tics,” he added, “we believe these were transient.”<sup>73</sup>

■ Although a 30% response rate “could have an impact on selection bias,” it’s impossible to know which way the bias may have gone. Parents with concerns about their child’s development might be more likely to participate.

**SUMMARY:** The response rate to this study was extremely low, suggesting possible selection bias in the recruitment of patients. Moreover, the children were examined years after their thimerosal exposure, and many of them had presumably received medical and behavioral treatments in the intervening period. It is illogical to conclude there is “no causal association” between thimerosal neuropsychological deficits, and then cite an increased risk for tics (one replicated in a prior study “further study”) and increased language deficits (also found in the same prior study).

## **7) “Continuing increases in autism reported to California's developmental services system: mercury in retrograde.”<sup>74</sup>**

**Authors:** Schechter R, Grether JK.

**Publication and Date:** *Archives of General Psychiatry*, January, 2008

**Online at:** <http://archpsyc.ama-assn.org/cgi/content/full/65/1/19>

**Details:** “The exclusion of thimerosal from childhood vaccines in the United States was accelerated from 1999 to 2001.” This study was designed to see if trends in California’s Department of Developmental Services (DDS) autism client data “support the hypothesis that thimerosal exposure is a primary cause of autism.” The authors investigated trends in autism cases by age and birth cohort in children with autism who were DDS clients from January 1, 1995, through March 31, 2007.

**Results:** “The estimated prevalence of autism for children at each year of age from 3 to 12 years increased throughout the study period. The estimated prevalence of DDS clients aged 3 to 5 years with autism increased for each quarter from January 1995 through March 2007. Since 2004, the absolute increase and the rate of increase in DDS clients aged 3 to 5 years with autism were higher than those in DDS clients of the same ages with any eligible condition including autism.

**Authors’ Conclusions:** The DDS data do not show any recent decrease in autism in California despite the exclusion of more than trace levels of thimerosal from nearly all childhood vaccines. The DDS data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism.

### **CRITIQUES OF THE STUDY**

**Thimerosal Removal Not Complete Until 2003** – The authors’ statement that “The exclusion of thimerosal from childhood vaccines in the United States was accelerated from 1999 to 2001” is inaccurate. Vaccine makers were asked to voluntarily remove thimerosal from childhood vaccines in July of 1999, a process that took a few years. Likewise, the authors claim their study is inconsistent with a thimerosal association because “the prevalence of autism in children reported to the DDS has increased consistently for children born from 1989 through 2003, inclusive of the period when exposure to TCVs has declined.” The last TCVs (with the exception of the influenza vaccine) were manufactured in 2001, but expired in 2003.

**Youngest Cohort Data is Unreliable** – The study states that there were more 3-5-year olds in the first quarter of 2007 (children born from 2002-2004) than among 3-5 year olds in the first quarter of 2006 (born from 2001-2003). But diagnoses among younger children can vary, depending especially on the average age of diagnosis in any given area. This is why the CDC waits until children are 8 years of age in order to conduct its own autism surveillance studies, which are considered to be the most accurate in the

United States. Unfortunately, the CDC surveillance system does not include children in California.

**Falling Age of Diagnosis Creates Artificial Increase** – One reason that CDC waits until children are 8 years of age is because each year, the average age of autism diagnoses goes down. The result is that, each year, more and more three-year-olds are diagnosed as compared to prior years. This is supported by a study published in the December 2008 issue of *Archives of Pediatric and Adolescent Medicine*.<sup>75</sup> “Shifts in age at diagnosis inflated the observed prevalence of autism in young children in the more recent cohorts compared with the oldest cohort,” the authors wrote. “This study supports the argument that the apparent increase in autism in recent years is at least in part attributable to decreases in the age at diagnosis over time.”

**IOM: California Data Not Reliable For Incidence Studies** – In its 2004 report on thimerosal and autism, the IOM Immunization Safety Committee discussed two reports from California’s DDS system (from 1999 and 2003) that showed a large increase in autism cases from 1987 to 2002. Those data were “widely cited as evidence of an increase in the incidence of ASD in the United States,” the panel wrote. But, it cautioned: “The report stresses that the study was not designed to measure trends in autism incidence, and the data should therefore be interpreted with caution. Several methodological limitations have been cited, including the failure to account for changes over time in the population size or composition, in diagnostic concepts, in case definitions, or in *age of diagnosis*.” (Emphasis added).

**DDS: Be Careful Drawing Conclusions** – On a webpage titled “Data Interpretation Considerations and Limitations,” the DDS cautions: “Although information published by DDS in the Quarterly Client Characteristics Report is often used by media and research entities to develop statistics and draw conclusions some of these findings may misrepresent the quarterly figures.” In addition, it says, “Increases in the number of persons reported from one quarter to the next do not necessarily represent persons who are new to the DDS system.”<sup>76</sup>

**Authors: Findings Must Be Confirmed** – The authors concluded that “Continuing evaluation of the trends in the prevalence of autism for children born in recent years is warranted to confirm our findings.” Unfortunately, that will never be possible in California, where entry criteria for DDS services were broadly expanded to include children with PDD-NOS and Asperger’s Disorder in January, 2008. “Information from these new items will not be comparable to prior information,” a DDS statement says.

**SUMMARY** – The conclusions of this study rely solely on one year of data in one state among the youngest children who presumably received markedly less thimerosal in their vaccines. Basing such a conclusion on the youngest cohort data is unreliable, partly because the falling age of diagnosis creates an artificial increase. The IOM said the California data is not reliable for incidence studies, the California Department of Developmental Services cautioned against drawing conclusions from the database, and



the authors themselves warned that their findings must be confirmed from later data, something that has not happened – and cannot happen.

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