

SOMETHING IS ROTTEN IN DENMARK

**Analysis of the Social Network of Authors in Four Recent Articles
on Autism, Mercury and Selected Childhood Vaccine Exposures**

and

**Assessment of the Role, Influence and Interests of the Statens
Serum Institute in Issues of Vaccine Safety Studies**

Safe Minds

October, 2003

SUMMARY (1)

Three recent studies based on data from a Danish patient registry have attempted to refute the link between mercury-containing vaccines and autism. These studies comprise the output of a deliberate and coordinated plan to attack the autism-mercury connection. Following behind a similar Danish registry analysis of the autism-MMR vaccine link, these three studies were all

- published in rapid succession in prestigious journals**
- based on slightly different (but analytically non-comparable) views of the same event**
- prepared by author groups with substantial connections and overlaps**

These author groups comprise a social network with strong personal and institutional ties. These ties create a significant conflict of interest that was not reported in any of the journals. The entire author network has ties to a for-profit, Danish vaccine manufacturer: the Statens Serum Institut (SSI). SSI authors hold positions of substantial influence in the author network, while SSI occupies a central position of leadership in the network of participating institutions

- SSI directly employs over one-third (6 of 17) of the study authors**
- SSI “houses the central unit of the Danish Epidemiology Science Centre”, the employer for the first authors of 2 of 3 studies, and for 7 of 17 of the authors (four of whom are not directly employed by SSI)**
- SSI staff have co-authored at least six additional studies with two employees of the Danish National Centre for Register-based Research**
- CDC employees and consultants make up the largest non-Danish group (3 of 17)**

This collection of three articles, more appropriately viewed as a single networked initiative dominated by SSI, were therefore directly influenced by the financial interests of a manufacturer of final products (historically) and components (currently) for thimerosal-containing vaccines.

SUMMARY (2)

SSI is a for-profit, state-owned enterprise with roughly \$120 million in annual revenue. They report income statement and balance sheet information, including measures of return on invested capital. Their research activities support their business interests

The commercial interests of SSI are strongly tied to the success of their vaccine products and, especially to their exports outside Denmark

- **vaccines represent half of SSI's revenues and over 80% of its profits**
- **vaccine exports appear highly profitable and represent SSI's fastest growing business segment**
- **important export markets include the United States and the United Kingdom, home to active vaccine safety controversies**

SSI has a direct financial interest in the autism-mercury controversy, with possible product liability due to their past production and revenue risk based on the demand for their intermediate products.

- **SSI manufactured the (now discontinued) mono-component pertussis vaccine under investigation in the three studies**
- **SSI exports diphtheria and tetanus toxoid products used in thimerosal-containing vaccines still sold in the United States and the United Kingdom**

A HIGHLY CONNECTED AUTHOR NETWORK

Four articles from Denmark have examined autism vaccine controversies. Three of these have recently addressed the autism-mercury connection

The author network involved in preparing these studies is highly connected

- **most authors work in Denmark**
- **many authors participated in more than one study and provide strong links across all four studies**
- **a few key institutions provide the home for the majority of the network**
- **Statens Serum Institut (SSI) employees play a central role in the network**

Most network participants either work directly for SSI or work for institutions with strong ties to SSI

FOUR ARTICLES FROM DENMARK

NEW ENGLAND JOURNAL OF MEDICINE

A population-based study of measles, mumps, and rubella vaccination and autism

**N Engl J Med.
2002;347(19):1477-82**

**Madsen KM
Hviid A
Vestergaard M
Schendel D
Wohlfahrt J
Thorsen P
Olsen J
Melbye M**

AMERICAN JOURNAL OF PREVENTIVE MEDICINE

Autism and thimerosal-containing vaccines: lack of consistent evidence for an association.

**Am J Prev Med.
2003;25(2):101-6**

**Stehr-Green P
Tull P
Stellfeld M
Mortenson PB
Simpson D**

PEDIATRICS

Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data.

**Pediatrics.
2003;112(3 Pt 1):604-6**

**Madsen KM
Lauritsen MB
Pedersen CB
Thorsen P
Plesner AM
Andersen PH
Mortensen PB**

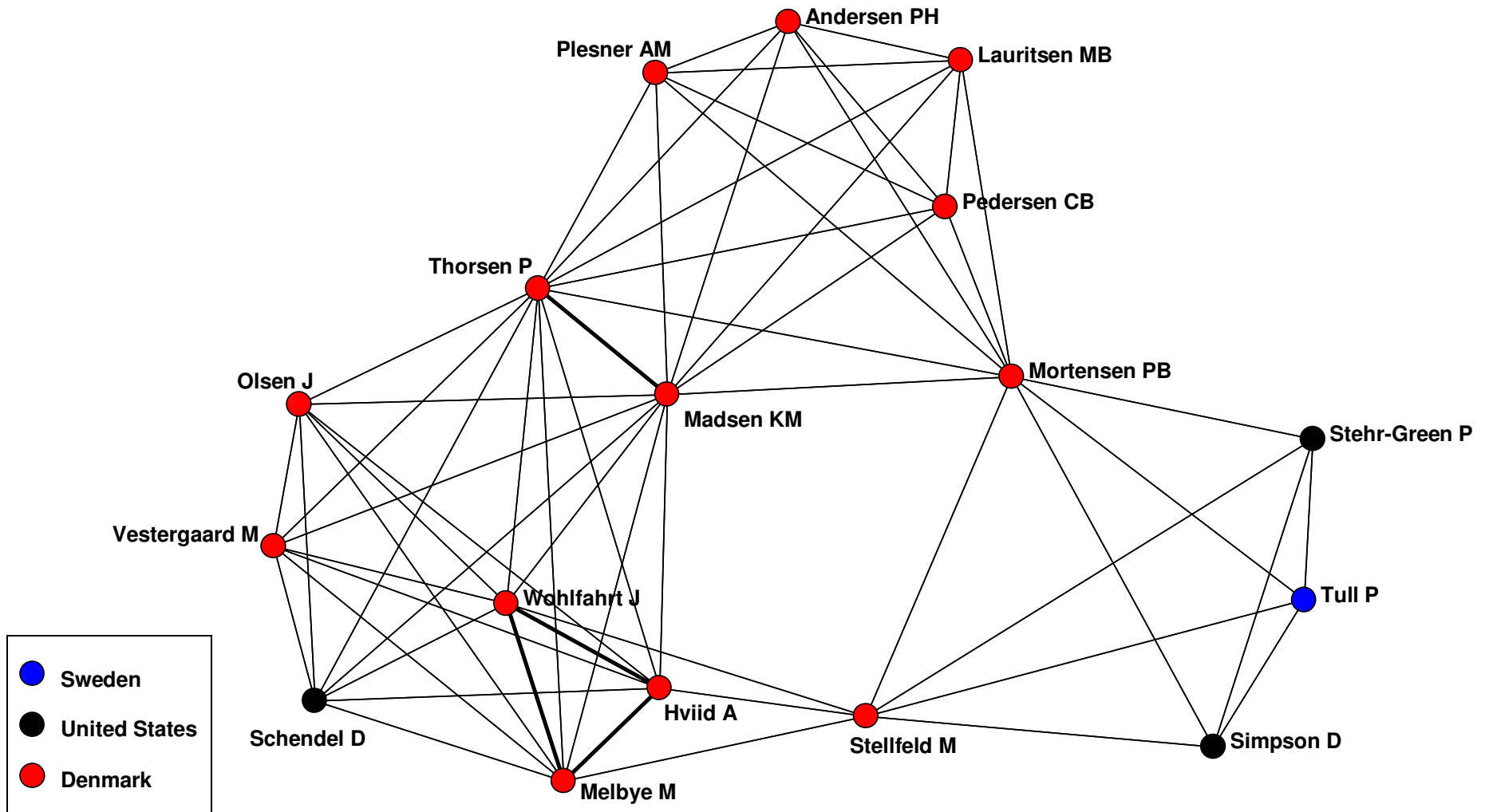
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Association between thimerosal-containing vaccine and autism

**JAMA.
2003;290(13):1763-6**

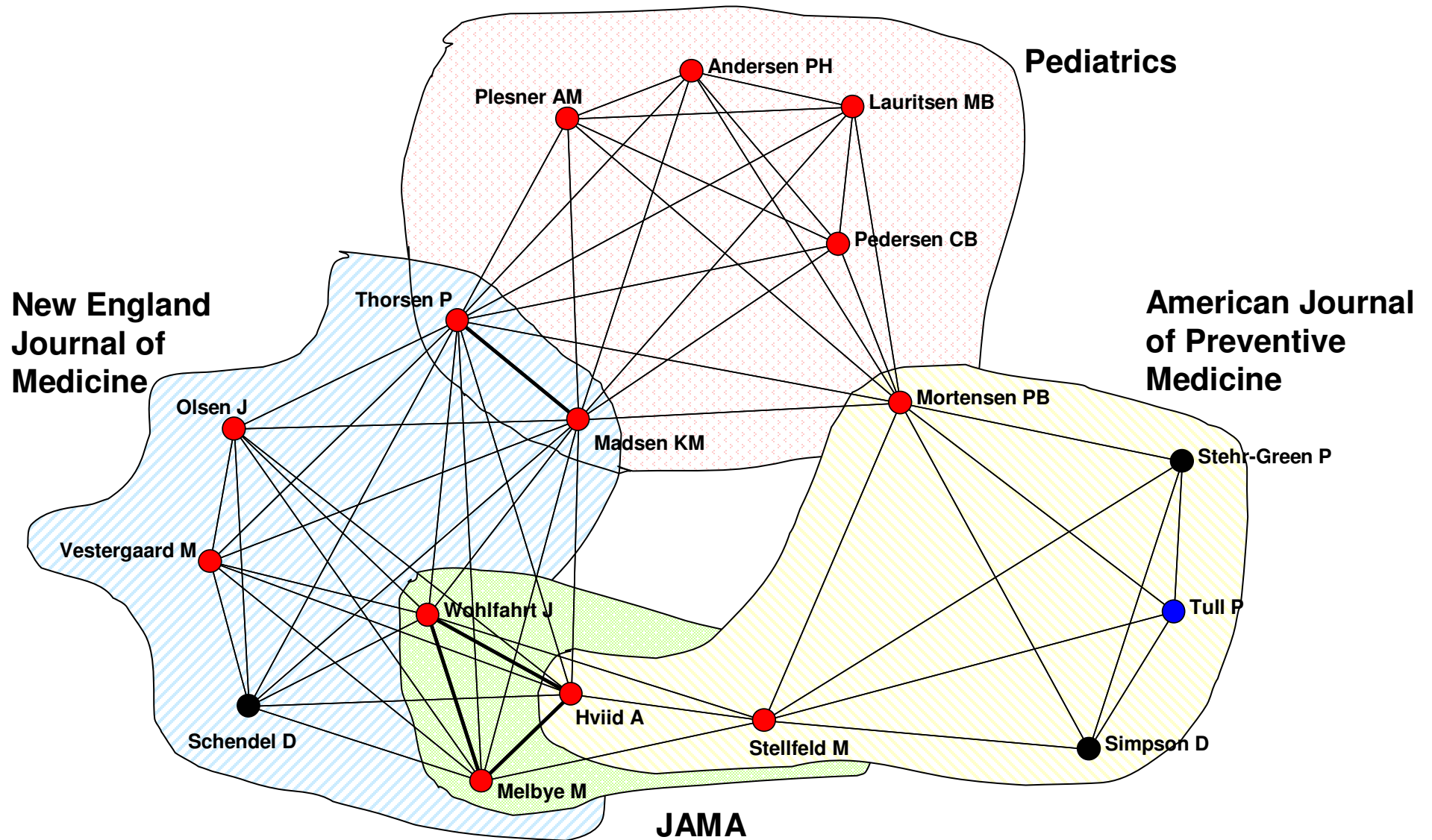
**Hviid A
Stellfeld M
Wohlfahrt J
Melbye M**

AUTHORS BY COUNTRY



Note: Thicker line means authors have written two papers together

AUTHORS BY COUNTRY AND JOURNAL



KEY AUTHOR AFFILIATIONS

***Danish Epidemiology Science Centre (DESC)
Department of Epidemiology and Social Medicine
University of Aarhus, Aarhus, Denmark***

**Jorn Olsen, M.D. (DESC leader)
Kreesten M. Madsen, M.D.
Poul Thorsen M.D.
Mogens Vestergaard, M.D.**

***Danish Epidemiology Science Centre (DESC)
Department of Epidemiology Research
Statens Serum Institut, Copenhagen, Denmark***

**Mads Melbye, M.D. (Department head)
Anders Hviid, M. Sc.
Jan Wohlfahrt, M.Sc.**

***Department of Medicine
Statens Serum Institut, Copenhagen, Denmark***

**Michael Stellfeld, M.D. (Department head)
Peter H. Andersen, M.D.
Ann-Marie Plesner, M.D. Ph.D.**

***National Centre for Register-based Research
University of Aarhus, Aarhus, Denmark***

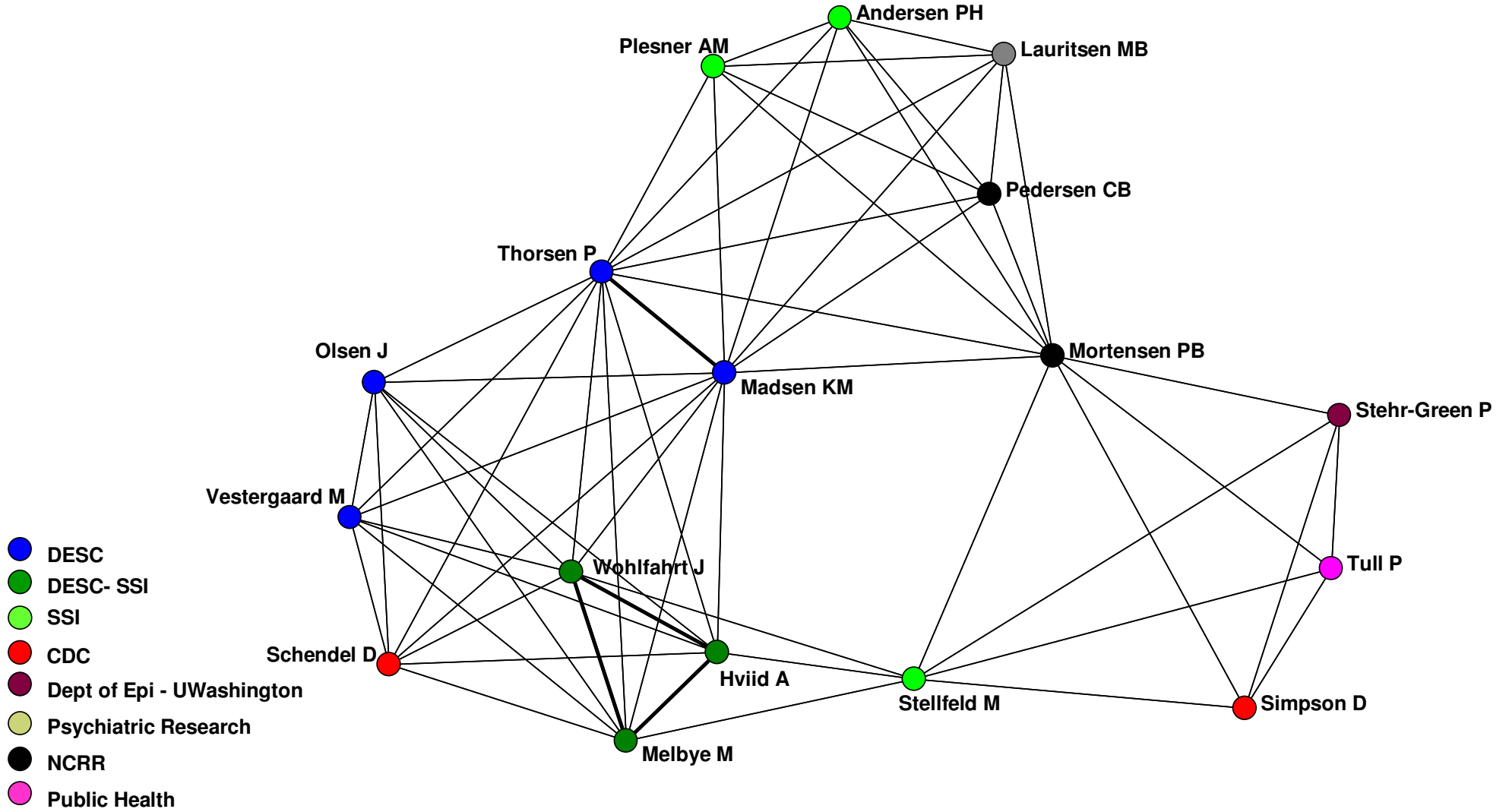
**Preben-Bo Mortensen, Dr. Med. Sc.
Carsten B. Pedersen, M.Sc.**

***Centers for Disease Control and Prevention
Atlanta GA, USA***

**Diane Simpson, M.D. Ph.D. (NIP)⁽¹⁾
Diana Schendel, Ph.D. (NCBDDD)⁽²⁾
Paul Stehr-Green, Dr.P.H. M.P.H. (consultant)**

- (1) National Immunization Program
(2) National Center on Birth Defect and Developmental Disabilities

AUTHORS BY ORGANIZATION

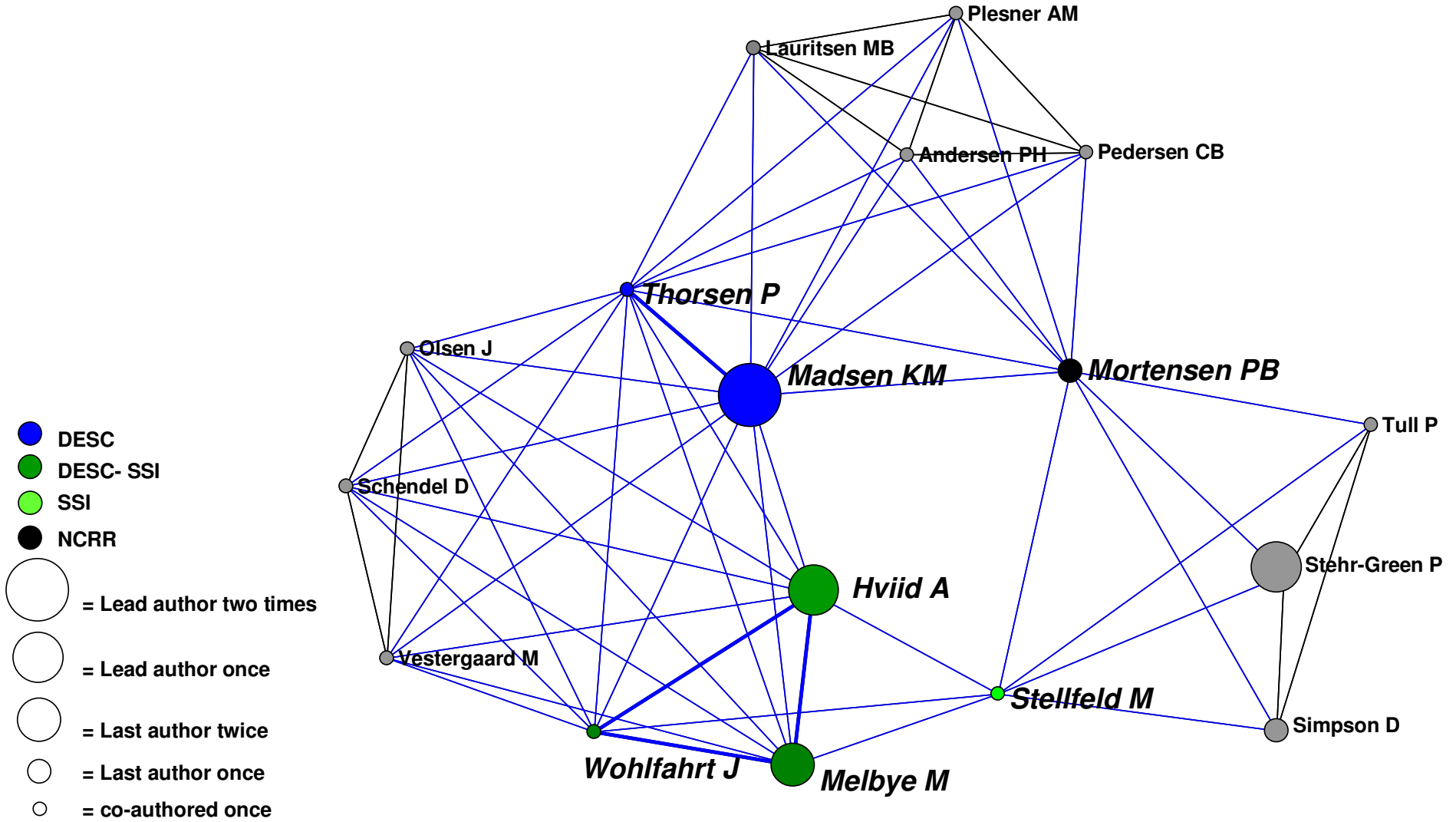


MEASURES OF AUTHOR CENTRALITY IN THE NETWORK

Degree Centrality ⁽¹⁾		Betweenness Centrality ⁽²⁾		Closeness Centrality ⁽³⁾		Eigenvector Centrality ⁽⁴⁾	
Madsen KM	13	Mortensen PB	26.10	Madsen KM	80.00	Madsen KM	0.38
Thorsen P	13	Madsen KM	16.30	Thorsen P	80.00	Thorsen P	0.38
Hviid A	10	Thorsen P	16.30	Mortensen PB	72.73	Hviid A	0.34
Melbye M	10	Stellfeld M	15.40	Hviid A	66.67	Melbye M	0.34
Mortensen PB	10	Hviid A	3.30	Melbye M	66.67	Wohlfahrt J	0.34
Wohlfahrt J	10	Melbye M	3.30	Wohlfahrt J	66.67	Olsen J	0.26
Olsen J	7	Wohlfahrt J	3.30	Stellfeld M	64.00	Schendel D	0.26
Schendel D	7	Andersen PH	0.00	Andersen PH	61.54	Vestergaard M	0.26
Stellfeld M	7	Lauritsen MB	0.00	Lauritsen MB	61.54	Mortensen PB	0.19
Vestergaard M	7	Olsen J	0.00	Pedersen CB	61.54	Andersen PH	0.16
Andersen PH	6	Pedersen CB	0.00	Plesner AM	61.54	Lauritsen MB	0.16
Lauritsen MB	6	Plesner AM	0.00	Olsen J	57.14	Pedersen CB	0.16
Pedersen CB	6	Schendel D	0.00	Schendel D	57.14	Plesner AM	0.16
Plesner AM	6	Simpson D	0.00	Vestergaard M	57.14	Stellfeld M	0.15
Simpson D	4	Stehr-Green P	0.00	Simpson D	51.61	Simpson D	0.05
Stehr-Green P	4	Tull P	0.00	Stehr-Green P	51.61	Stehr-Green P	0.05
Tull P	4	Vestergaard M	0.00	Tull P	51.61	Tull P	0.05

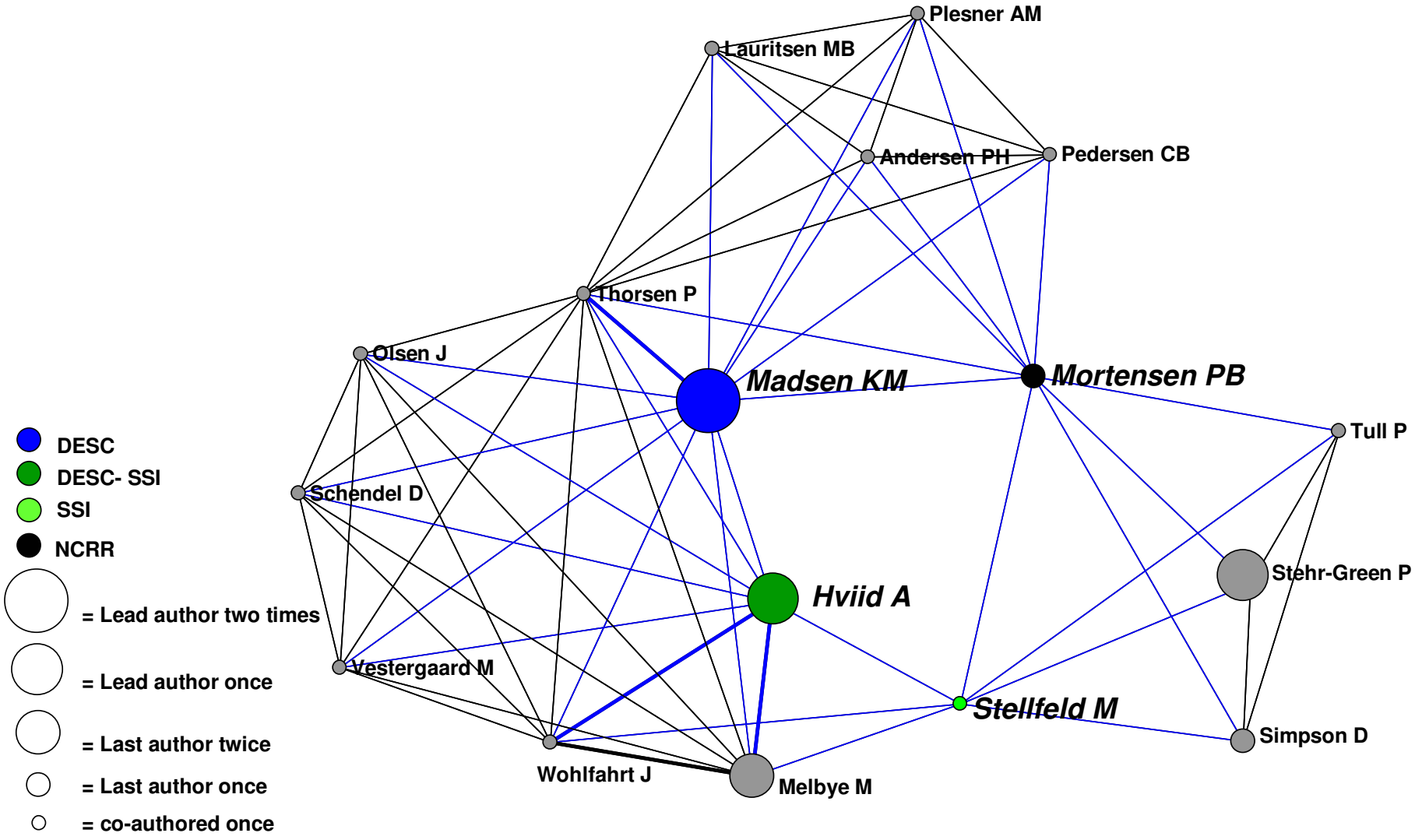
- (1) High degree centrality means that author connects to many other nodes
- (2) High betweenness centrality means others have to go through this author often to connect to others
- (3) High closeness centrality means that the author is close to many others in the network
- (4) High eigenvector centrality means that the author is connected to other authors who are well connected

SEVEN CORE AUTHORS WITH HIGHEST SCORES FOR BETWEENNESS AND CLOSENESS



Note: Thicker line means authors have written two papers together

FOUR CORE AUTHORS CONNECT KEY ORGANIZATIONS



Note: Thicker line means authors have written two papers together

LINKS BETWEEN KEY ORGANIZATIONS (1)

Statens Serum Institute (SSI), Department of Epidemiology Research and University of Aarhus Department of Epidemiology and Social Medicine

*The Danish Epidemiology Science Centre was established in 1994 by the National Research Foundation. The Centre has 3 research units in Denmark located at **Statens Serum Institut**, Kommunehospitalet, Copenhagen and the **University of Aarhus**, respectively.*

*The board of the Centre is **Jørn Olsen** (Head), **Mads Melbye**, Thorkild IA Sørensen and Peter Aaby.*

-Danish Epidemiology Science Center, <http://www.epidemiology.dk/>

The Department [of Epidemiology Research at SSI] furthermore houses the central unit of the Danish Epidemiology Science Centre, which was established as a network collaboration with two other institutions in Denmark, Department of Epidemiology and Social Medicine, Aarhus University, and Institute of Preventive Medicine, Copenhagen Hospital Corporation

-Statens Serum Institut, Department of Epidemiology Research

http://www.serum.dk/graphics/html/epiresearch/docs/main_intro.html

LINKS BETWEEN KEY ORGANIZATIONS (2)

Department of Epidemiology and Social Medicine, University of Aarhus and
National Centre for Registry-based Research, University of Aarhus

Weekly gatherings

Furthermore, the [National] Centre [for Register-based Research] is involved in the seminars held every week at the **Department of Epidemiology and Social Medicine**, Aarhus University. The seminars take place every Friday morning at 9.00 in Building 261, 'Lunch room', at the ground floor.

-NCRR web-site, http://www.ncrr.au.dk/html/nyhedsbrev/nyhedsbrev_eng.htm

University of Aarhus research centers sponsored by the Danish National Research Foundation

During the past year the University of Aarhus has been host to the following centres, which are all operating on five-year grants from the Danish National Research Foundation.... **The Danish Epidemiology Science Centre** was established in 1994 with a grant from the Danish National Research Foundation. The Centre has research sections at the University of Aarhus, the Institute of Preventative Medicine in Copenhagen, **Statens Serum Institut** (the National Central Laboratory of the Danish Health System) and in Guinea Bissau.... **Head of Centre: Professor Jørn Olsen, PhD**

The **National Centre for Register-based Research** opened on 1 September 2000 within the Faculty of Social Sciences at the University of Aarhus, occupying newly-renovated premises in the old Sahva Building at the former Orthopaedic Hospital... The Centre has a grant from the Danish National Research Foundation to finance its first five years of operation. After that, if the Centre is a success, it will be integrated into the structure of the University of Aarhus in some form or another. ... **Head of Centre: Professor Preben Bo Mortensen, dr.med**

-University of aarhus web-site, <http://www.au.dk/en/research/arep2000.htm>

LINKS BETWEEN KEY ORGANIZATIONS (3)

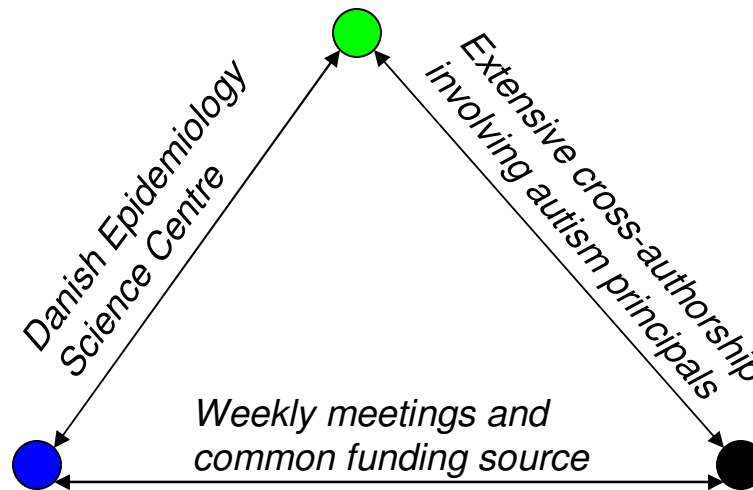
Statens Serum Institut (SSI), Department of Epidemiology Research and National Centre for Registry-based Research (NCRR), University of Aarhus

Six publications (excluding autism studies), in which autism principals from SSI and NCRR were co-authors

1. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med*. 1999;340(8):603-8.
Mortensen PB, (NCRR) Pedersen CB (NCRR), Westergaard T (SSI), Wohlfahrt J (SSI), Ewald H, Mors O, Andersen PK, Melbye M (SSI)
2. Risk factors for parvovirus B19 infection in pregnancy. *JAMA*. 1999;281(12):1099-105.
Valeur-Jensen AK, Pedersen CB, Westergaard T (SSI), Jensen IP, Lebech M, Andersen PK, Aaby P (SSI), Pedersen BN, Melbye M.
3. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. *Arch Gen Psychiatry*. 1999;56(11):993-8.
Westergaard T (SSI), Mortensen PB (NCRR), Pedersen CB (NCRR), Wohlfahrt J (SSI), Melbye M (SSI).
4. Cancer risk in a cohort of polio patients. *Int J Cancer*. 2001;92(4):605-8.
Nielsen NM (SSI), Wohlfahrt J (SSI), Aaby P (SSI), Hjalgrim H (SSI), Pedersen CB (NCRR), Askgaard DS, Melbye M (SSI).
5. Risk factors and confounders in the geographical clustering of schizophrenia. *Schizophr Res*. 2001;49(3):295-9.
Torrey EF, Mortensen PB (NCRR), Pedersen CB (NCRR), Wohlfahrt J (SSI), Melbye M. (SSI)
6. Sibships characteristics, influenza and risk of schizophrenia. A population-based cohort study. *Ugeskr Laeger*. 2001;163(35):4745-9.
Westergaard T (SSI), Mortensen PB (NCRR), Pedersen CB (NCRR), Wohlfahrt J (SSI), Melbye M (SSI)

INSTITUTIONAL TIES UNDERLIE AUTHOR NETWORK

**Statens Serum Institut
(Drs. Mads Melbye
and Michael Stellfeld)**



**University of Aarhus
Department of Epidemiology
and Social Medicine
(Professor Jorn Olsen)**

**National Centre for
Register-based Research
(Professor Preben-Bo Mortensen)**

THE COMMERCIAL INTERESTS OF STATENS SERUM INSTITUT

Key leaders of the author network occupy leadership positions in SSI

The vaccine division plays a critical role in the financial performance of the company

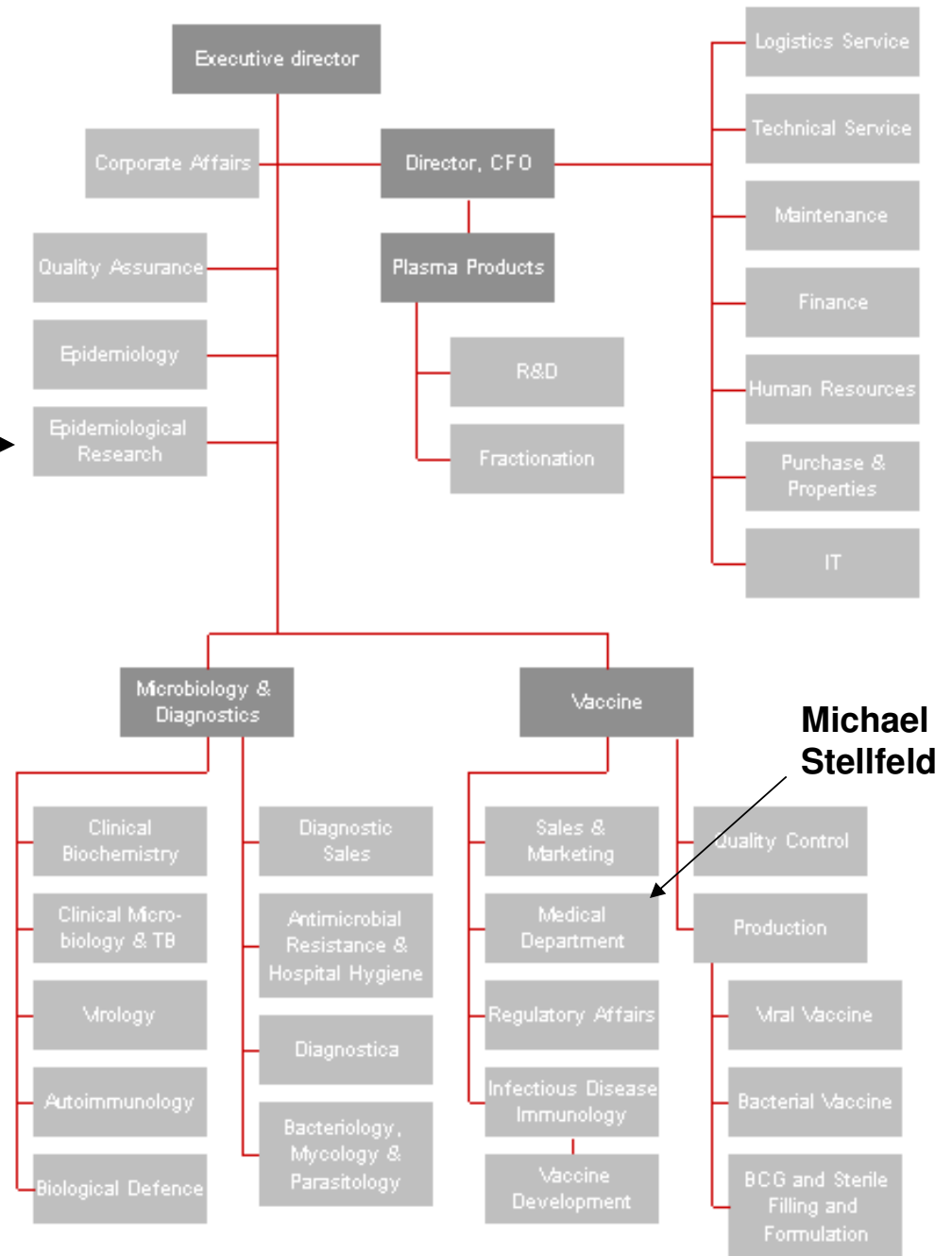
- **half of revenues and over 80% of profits**
- **vaccine exports are the fastest growing and (possibly) most profitable segment of SSI's business**
- **mercury-containing products play a significant role in the financial outlook for SSI's vaccine export business**
- **SSI provides vaccine ingredients for mercury-containing vaccines currently in use in the United States and the United Kingdom**

SSI has a direct financial stake in assessments of vaccine safety

- **revenues could decline sharply if DT and TT products are recalled or discontinued**
- **product liability issues could arise if past vaccine production is linked to autism**

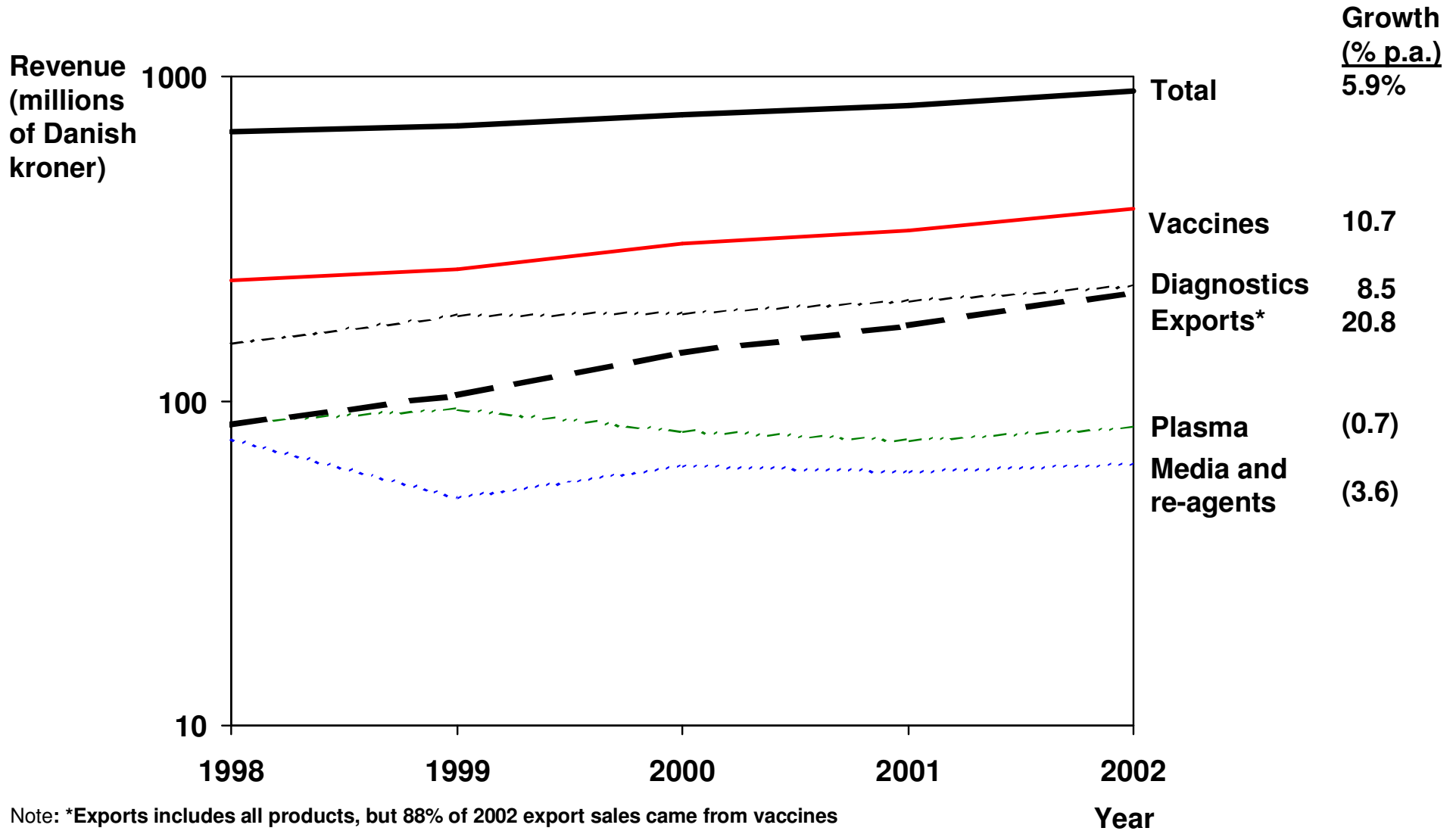
STATENS SERUM INSTITUT ORGANIZATION CHART

Mads Melbye →



Michael Stellfeld

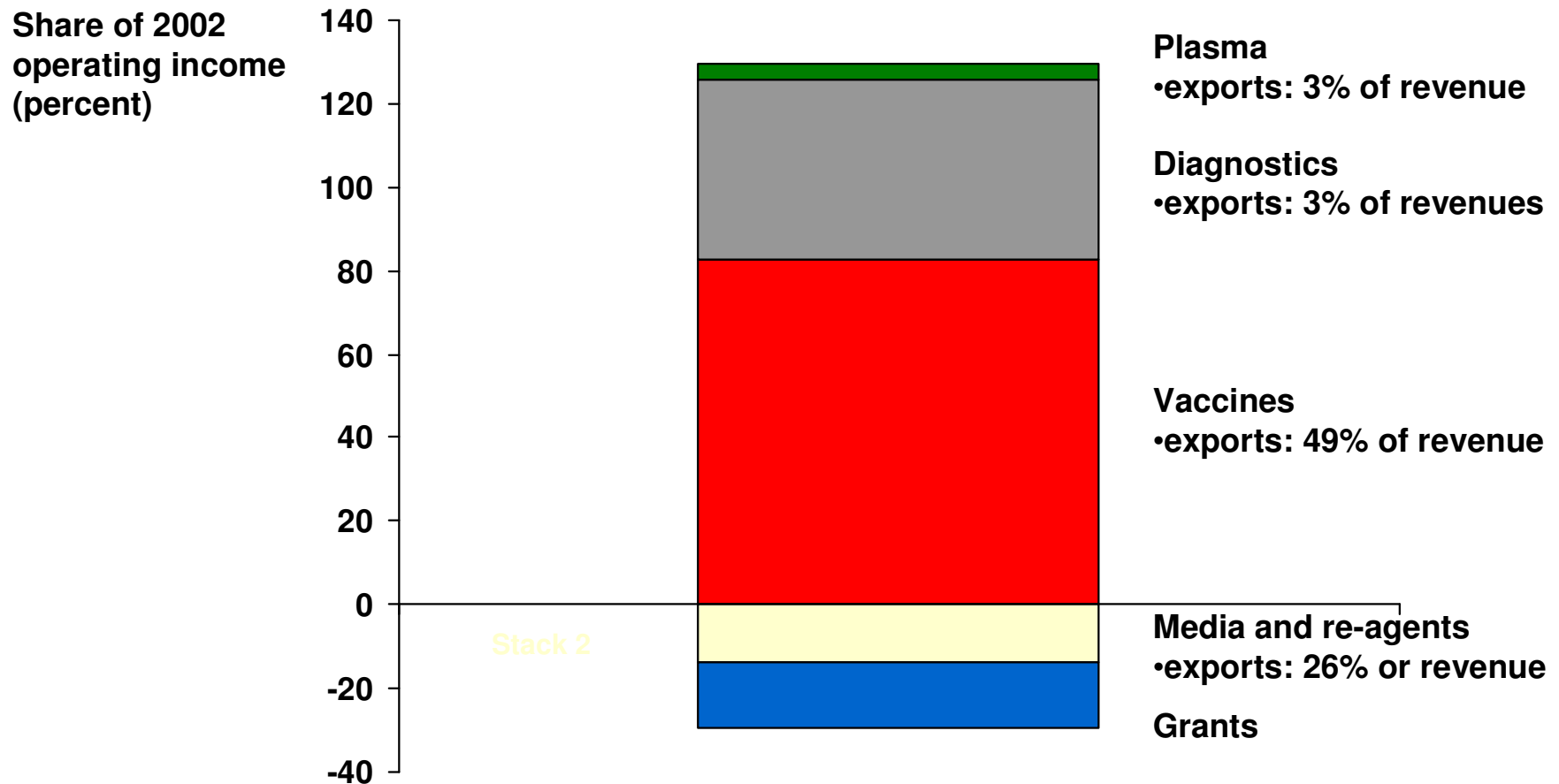
STATENS SERUM INSTITUT REVENUE GROWTH DRIVEN BY VACCINES AND (MOSTLY VACCINE) EXPORTS



Note: *Exports includes all products, but 88% of 2002 export sales came from vaccines

Source: Statens Serum Institut, 2002 Annual Report

OVER 80% OF STATENS SERUM INSTITUT'S 2002 PROFIT CAME FROM VACCINES, INCLUDING SIGNIFICANT EXPORT SALES



Source: Statens Serum Institut, 2002 Annual Report

STATENS SERUM INSTITUT VACCINE DIVISION DEDICATES SUBSTANTIAL RESOURCES TO GROWING EXPORT MARKETS

Vaccine production departments	Vaccine products	Customers and markets
<p>Viral vaccine department (42 employees, single unit)</p>	<ul style="list-style-type: none"> •Injected polio vaccine (IPV) 	<ul style="list-style-type: none"> •Danish government for domestic IPV program •Working on U.S. FDA approval
<p>Bacterial vaccine department (30 employees, 4 units)</p> <ul style="list-style-type: none"> • Tetanus unit • Diphtheria unit • Media unit <p>• Toxoid development unit</p>	<ul style="list-style-type: none"> •Tetanus toxoid •Diphtheria toxoid •Growth and culture media, buffers for virus and bacteria cultivation •Toxoid development 	<ul style="list-style-type: none"> •Denmark, U.S. and Europe •Denmark, U.S. and Europe •Denmark, U.S. and Europe <p>•Internal</p>
<p>BCG and sterile filling and formulation department (55 employees, 3 units)</p> <ul style="list-style-type: none"> • Sterile unit • BCG unit • Packing unit 	<ul style="list-style-type: none"> •BCG vaccine for tuberculosis •BCG culture for bladder cancer •Preparation and packaging for all SSI vaccine products and exports 	<ul style="list-style-type: none"> •Danish government and “export trade”

STATENS SERUM INSTITUT PROVIDES COMPONENTS FOR DT, TT AND DTaP VACCINES IN THE UNITED STATES



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Reference Numbers: 95-1530, 95-1531 and 95-1532

Ms. Brigitte W. Knudsen
Statens Seruminstitut
5, Artillerivej
DK-2300 Copenhagen S
DENMARK

JUL 29 1998

Dear Ms. Knudsen:

This letter hereby issues Department of Health and Human Services Biologics License No. 1255 to Statens Seruminstitut, Copenhagen, Denmark, in accordance with the provisions of Section 351(a) of the Public Health Service Act as amended November 21, 1997 (FDAMA; Public Law 105-115), controlling the manufacture and sale of biological products. This license authorizes you to manufacture and import into this country to ship for sale, barter, or exchange those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the products Tetanus Toxoid Concentrate (For Further Manufacturing Use) and Diphtheria Toxoid Concentrate (For Further Manufacturing Use) to be shipped to North American Vaccine, Inc., in a shared manufacturing arrangement for the manufacture of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP).

STATENS SERUM INSTITUTE PROVIDES UNITED KINGDOM STANDARDS FOR TETANUS AND DIPHTHERIA TOXOIDS



Assuring the quality of biological medicines

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enquiries@nibsc.ac.uk
<http://www.nibsc.ac.uk>

The 1st International Reference Reagent for TETANUS TOXOID FOR FLOCCULATION TEST

Code: **TEFT**

(Version 02)

1. INTRODUCTION

This material has been prepared and characterised by the Statens Serum Institut (SSI), Copenhagen, Denmark. With effect from 1st July 1997, the National Institute for Biological Standards and Control (NIBSC), Potters Bar, UK is the custodian and distributor of this material.

The 1st International Reference Reagent for DIPHTHERIA TOXOID FOR FLOCCULATION TEST

Code: **DIFT**

(Version 02)

1. INTRODUCTION

This material has been prepared and characterised by the Statens Serum Institut (SSI), Copenhagen, Denmark. With effect from 1st July 1997, the National Institute for Biological Standards and Control (NIBSC), Potters Bar, UK is the custodian and distributor of this material.

The package insert from SSI is attached.

STATENS SERUM INSTITUT DESCRIBES ITS REVENUE AND LIABILITY FINANCIAL STAKE IN VACCINE RISKS

RISKS

Vaccines

As a biological production, vaccine production, the main pillar in the development of revenue, is sensitive. For example, cultivation problems can occur as a consequence of quite small changes in the cultivation conditions. Some problems often emerge late in the production process, so rejects include not only raw materials but also the supplies and the work input.

Insurance

The Institute's product liability insurance is expected to lead to a significant increase in expenses the coming years.

CONCLUSION

The recent series of articles on mercury and autism and Denmark were conducted and sponsored by a single network of authors.

Those authors were tied, either indirectly or as employees, to a for-profit vaccine manufacturer (SSI) with a direct financial interest in the outcome of the analysis. Their motivations as investigators were closely tied to the products they were investigating. They have a clear conflict of interest.

Statens Serum Institut relies heavily on its vaccine products for revenue, growth and profitability. The growth and profitability, in particular, of its export vaccine business provides strong incentives for SSI to build ties with public health officials and manufacturing partners in the United States and United Kingdom. SSI has a clear and strong interest in the policy debates surrounding the autism-mercury controversy. They cannot be considered an objective party.

SSI has a direct financial interest in the assessment of past mercury-containing vaccine safety issues and the future viability of mercury-containing products. Their participation in any analysis directly compromises the investigation. They should be excluded from further work in vaccine safety assessment.