Exhibit 12

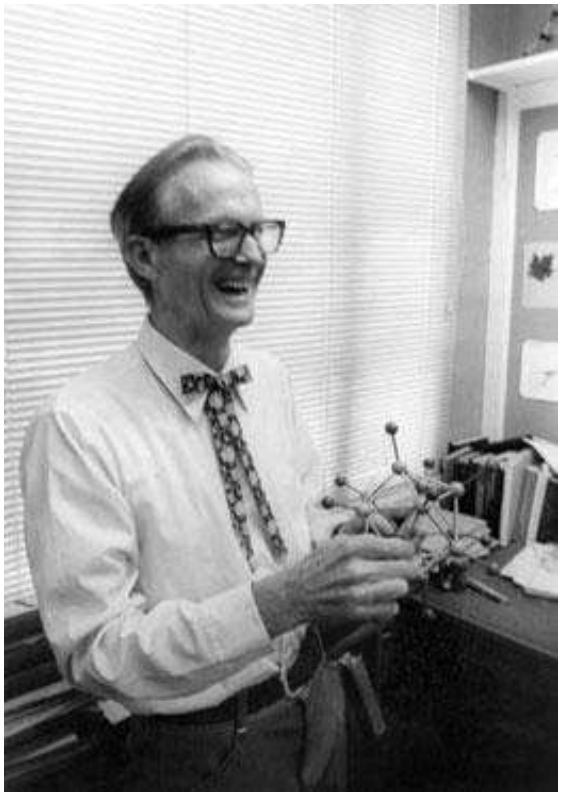
People

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**) 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

Poul Thorsen PubMed Bibliography 1991-2017
(Pre and Post Indictment)
Notes on US Government *Employee and **Funding are Noted in Red

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List as of 7/5/2017. (PubMed provides a 1985 physics article during search that is not Poul Thorsen's.)

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

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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) 1β, tumour necrosis factor (TNF) α, 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.[1,2] 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.[3] 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[4] 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[5]).

A large body of evidence suggests that infection of the reproductive tract is an important cause of PTD.[6–11] In specific studies, evidence for upper reproductive tract infection involving the maternal/fetal unit such as histological chorioamnionitis,[12] infected amniotic fluid, and markers of infection detected from the amniotic fluid,[13,14] have been associated with PTD. Several studies have also found associations between infections of the lower reproductive tract, such as *Chlamydia trachomatis* (CT),[15–17] bacterial vaginosis (BV)[18,19] and *Streptococcus agalactiae* (group B streptococcus, GBS),[20] and adverse outcome of pregnancy. *Trichomonas vaginalis*,[21] *Gardnerella vaginalis*,[22] *Escherichia coli*,[23] and anaerobic bacteria[22–24] have also been associated with PTD. Mycoplasmas, primarily *Mycoplasma hominis*, and *Ureaplasma urealyticum*, are still subject to great attention in relation to PTD;[11–25] most investigations indicate that *U. urealyticum* factors in upper reproductive tract infection may lead to an adverse outcome of pregnancy.[26,27] 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.[28] The strongest evidence for infections in association with LBW/PTD comes from effective intervention trials as carried out by Hauth *et al.*[29] and Morales *et al.*[30]

Pro-inflammatory cytokines (e.g. TNF-α, IL-1β, 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-1β was elevated in vaginal secretions among BV-positive pregnant women,[31] 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.[32] Pregnant women found culture-positive for bacteria in the amniotic fluid had elevated levels of IL-1β, TNF-α and IL-6 in the amniotic fluid.[33] Furthermore, IL-6 serum levels were elevated among women with preterm prelabour rupture of membranes with clinical or histological chorioamnionitis.[34]

Although initiation and immunomodulation of the primary inflammatory reaction are performed by the pro-inflammatory cytokines, the anti-inflammatory cytokines, such as IL-10,[35] IL-4,[36] and transforming growth factor β[37] 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.*[38] 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.*[39] In a small study by Hata *et al.*[40] 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-1β and TNF-α,[41] leading to the characteristic clinical spectrum characterising sepsis such as hypotension and organ dysfunction. An imbalance of cytokine function within the feto-placental unit might also explain an increased susceptibility to infections among a subset of pregnant women resulting in fetal expulsion.[42]

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-1β, TNF-α, 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°C. All participants were asked to fill out three questionnaires: the first at enrolment, a second at 30 weeks' gestation and

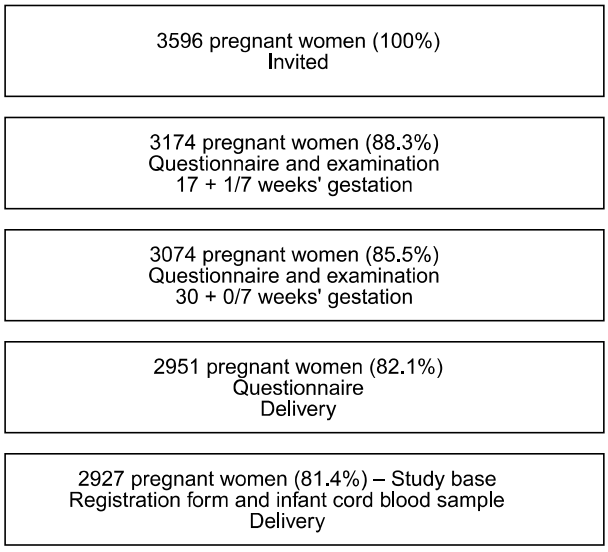

Figure 1. Odense cohort from enrolment until delivery.

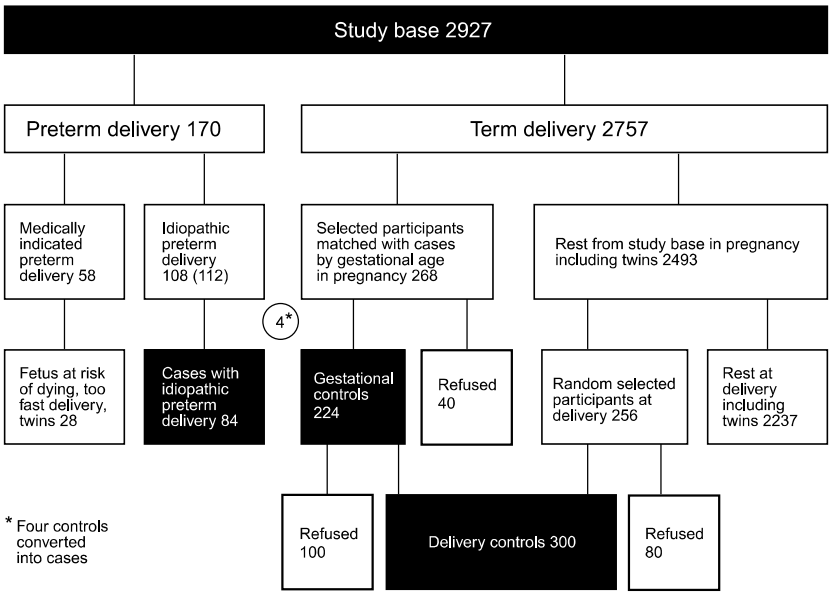

Figure 2. Design of the Odense Cohort nested case-control study involving 484 singleton pregnant women.

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

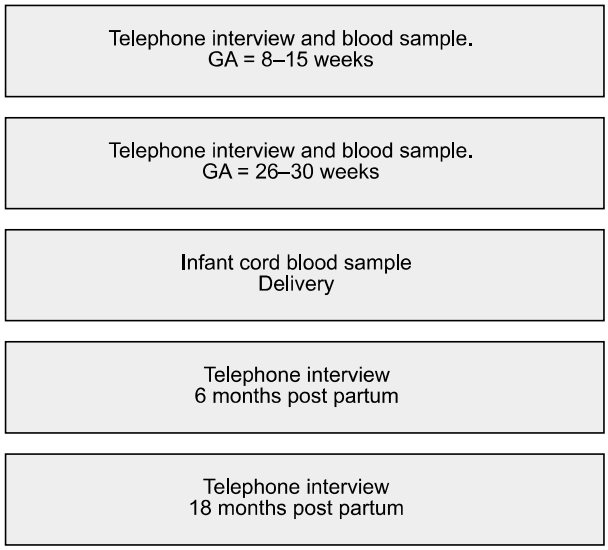

Figure 3. DNBC data collection from enrolment until post-partum follow-up. GA = gestational age.

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.

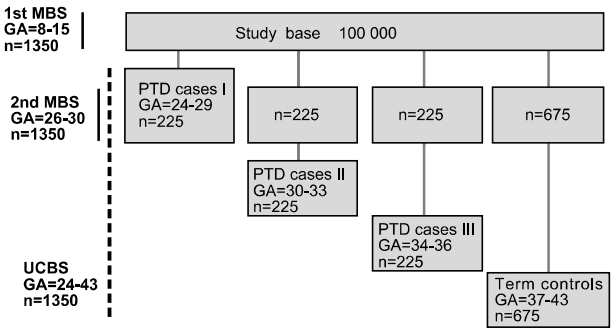

Figure 4. Design of the DNBC nested case-control study involving 1350 singleton pregnant women providing around 4050 samples. GA, gestational age in weeks; MBS, maternal blood sample; UCBS, umbilical cord blood sample; PTD, preterm delivery.

Selection of biological/biochemical markers and compartment

Biological/biochemical markers

The cytokines IL-1β, IL-6, IL-10, and TNF-α 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 oxytoxic 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-α) 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 ± SD: 16.9 ± 2.9 weeks for PTD cases vs. 16.4 ± 2.6 weeks for controls), in mid-pregnancy (mean ± SD: 34.2 ± 2.8 weeks for PTD cases vs. 32.5 ± 2.5 weeks for controls), and at delivery (mean ± SD: 34.2 ± 2.8 weeks for PTD cases vs. 40.3 ± 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.[43]

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°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°C.

Umbilical cord blood samples (5 mL) were obtained in dry, sterile tubes, cooled at room temperature for 1 h, cooled at 4°C temperature. Centrifuging and aliquoting were performed within 12 h from collection. The samples are stored at −80°C.

When the first measurement on the stored samples was to take place, the remainder of the aliquot was divided into tubes of 125 μL each and then stored at −80°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-1β, IL-6, TNF-α 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 R & D Systems (Minneapolis, MN). For each cytokine, the high sensitivity approach was employed. The assay methods are as follows:

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

Biomarkers	Vaginal fluid[a]	Maternal blood[a]	Fetal blood
Unspecific heat shock protein	X	X (enrolment)	
Chlamydia trachomatis-specific heat shock protein		X	
Prolidase	X		
Sialidase	X		
Anti *Gardnerella vaginalis* 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 α		X	X
Interleukin 1β		X	X
Interleukin 6	X	X	X
Interleukin 8	X		
Interleukin 10		X	

[a]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).[43] 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,[77] *Herpes simplex virus* type I and II, cytomegalovirus.

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-1β: stock solution of 8 pg/mL.
   (ii) TNF-α: 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 μL, 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 μL 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 μL 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 μL of substrate solution and incubated for 20 min at room temperature; (h) 50 μL of amplifying solution is added to each well for 30 min; (i) 50 μL 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-1β, IL-6, IL-10 and TNF-α 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.[43,44]

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 OCCC, 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-1β, IL-6, IL-10 and TNF-α, 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 $\geqslant 37$ weeks' gestation). The exposures to be studied are the concentrations of IL-1β, IL-6, IL-10 and TNF-α 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 decisions 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-1β and IL-6.[31,45,46] 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.[47] Unspecific HSP also increases cytokine production by macrophages.[48] 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[49] by modulating the level of IL-6 among others;[50] 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-α (tested on peripheral blood neutrophils)[49] and associated with PTD.[51,52]

Systemic factors associated with adverse outcome of pregnancy, mostly representing the maternal entity, such as relaxin,[53] have also been associated with adverse outcome of pregnancy. Petersen *et al.*[53] 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[6] or indirectly associated with cytokine actions.[54] Another and potent factor, corticotropin releasing hormone, has been associated with term and preterm parturition[55] and cytokine production.[56] 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.*[57] 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[58] and associated with PTD, particularly when detected in the second trimester.[59] A marker for monocyte activation, neopterin, increases after TNF-α injections[60] and might be associated with PTD, as reported in a study by Oleszczuk *et al.*[61]

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

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.[69] MBL has been associated with recurrent miscarriage possibly from cytokine imbalance within the feto-placental unit.[42]

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.[70–74]

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.[6,7,10,11,33,75,76] 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.

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Research Article

Public health issues related to infection in pregnancy and cerebral palsy

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Abstract

Cerebral palsy is the most common neuromotor developmental disability of childhood, affecting as many as 8,000 to 12,000 children born in the U.S. each year (corresponding to a prevalence rate of between 2 and 3 per 1000 children). Recent improvements in neonatal care have not resulted in a decline in the overall prevalence of cerebral palsy and, in fact, greater numbers of very preterm/very low birth weight infants are surviving with cerebral palsy and other developmental problems. Infection in pregnancy may be an important cause of the disorder. In preterm infants, there appears to be about a 2-fold increased risk for cerebral palsy from chorioamnionitis, and in term infants the estimated increased risk is about 4-fold. Provisionally, chorioamnionitis might account for 12% of spastic cerebral palsy in term infants and 28% of cerebral palsy in preterm infants. Studies of biochemical markers

of fetal inflammation typically associated with infection also suggest that an inflammatory response may be an important independent etiologic factor. If a substantial proportion of cerebral palsy is attributable to acute amnionitis infection and/or neonatal sepsis, cerebral palsy should have decreased in the United States after administration of intrapartum antibiotics became widespread in response to publication of public health consensus guidelines for Group B streptococcus in 1996. However, failure to detect declines could have a number of explanations and these explanations illustrate the many public health challenges related to intrauterine infection and cerebral palsy. Given the gaps in our current knowledge about intrauterine infection and cerebral palsy, public health recommendations for timely and specific prevention activities are limited at this time. MRDD Research Reviews 2002;8:39–45. © 2002 Wiley-Liss, Inc.

Exhibit 16

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A POPULATION-BASED STUDY OF MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM

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ABSTRACT

Background It has been suggested that vaccination against measles, mumps, and rubella (MMR) is a cause of autism.

Methods We conducted a retrospective cohort study of all children born in Denmark from January 1991 through December 1998. The cohort was selected on the basis of data from the Danish Civil Registration System, which assigns a unique identification number to every live-born infant and new resident in Denmark. MMR-vaccination status was obtained from the Danish National Board of Health. Information on the children's autism status was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals and outpatient clinics in Denmark. We obtained information on potential confounders from the Danish Medical Birth Registry, the National Hospital Registry, and Statistics Denmark.

Results Of the 537,303 children in the cohort (representing 2,129,864 person-years), 440,655 (82.0 percent) had received the MMR vaccine. We identified 316 children with a diagnosis of autistic disorder and 422 with a diagnosis of other autistic-spectrum disorders. After adjustment for potential confounders, the relative risk of autistic disorder in the group of vaccinated children, as compared with the unvaccinated group, was 0.92 (95 percent confidence interval, 0.68 to 1.24), and the relative risk of another autistic-spectrum disorder was 0.83 (95 percent confidence interval, 0.65 to 1.07). There was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autistic disorder.

Conclusions This study provides strong evidence against the hypothesis that MMR vaccination causes autism. (N Engl J Med 2002;347:1477-82.)

IT has been suggested that the measles, mumps, and rubella (MMR) vaccine causes autism.[1-4] The widespread use of the MMR vaccine has reportedly coincided with an increase in the incidence of autism in California,[5] and there are case reports of children in whom signs of both developmental regression and gastrointestinal symptoms developed shortly after MMR vaccination.[1] Measles virus has been found in the terminal ileum in children with developmental disorders and gastrointestinal symptoms but not in developmentally normal children with gastrointestinal symptoms.[6] The measles virus used in the MMR vaccine is a live attenuated virus that normally causes no symptoms or only very mild ones. However, wild-type measles can infect the central nervous system and even cause postinfectious encephalomyelitis, probably as a result of an immune-mediated response to myelin proteins.[7-9]

Studies designed to evaluate the suggested link between MMR vaccination and autism do not support an association, but the evidence is weak and based on case-series, cross-sectional, and ecologic studies. No studies have had sufficient statistical power to detect an association, and none had a population-based cohort design.[10-16] The World Health Organization and other organizations have requested further investigation of the hypothetical association between the MMR vaccine and autism.[2,17-20] We evaluated the hypothesis in a cohort study that included all children born in Denmark in 1991 through 1998.

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.). Address reprint requests to Dr. Madsen at the Danish Epidemiology Science Center, Department of Epidemiology and Social Medicine, Vennelyst Blvd. 6, DK-8000, Aarhus C, Denmark, or at kmm@dadlnet.dk.

METHODS

Study Design

We designed a retrospective follow-up study of all children born in Denmark during the period from January 1, 1991, to December 31, 1998. The cohort was established on the basis of data obtained from the Danish Civil Registration System and five other national registries.

All live-born children and new residents in Denmark are assigned a unique personal identification number (a civil-registry number), which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and family members (mother, father, and siblings).[21] The registry is updated once a week, and all changes in the stored information are reported to the registry according to established legal procedures. The civil-registry number is used as the link to information at the individual level in all other national registries. This system provides completely accurate linkage of information between registries at the individual level.

We determined MMR-vaccination status on the basis of vaccination data reported to the National Board of Health by general practitioners, who administer all MMR vaccinations in Denmark. The general practitioners are reimbursed by the state on the basis of these reports. We retrieved information on vaccinations from 1991 through 1999. The MMR vaccine was introduced in Denmark in 1987, and the single-antigen measles vaccine has not been used. The MMR vaccine used in Denmark during the study period was identical to that used in the United States and contained the following vaccine strains: Moraten (measles), Jeryl Lynn (mumps), and Wistar RA 27/3 (rubella).

The national vaccination program recommends that children be vaccinated at 15 months of age and again at 12 years. No change was made in the program during the study period. We obtained information on MMR vaccination at 15 months of age, since only this exposure is relevant to the end point under study. Since the vaccination data are transferred to the National Board of Health once a week, we chose Wednesday as the day of vaccination. When the vaccination information was recorded with the child's own civil-registry number, the information was directly linked with other registries. Before 1996, in most cases the vaccination information and the age of the child were recorded with the civil-registry number of the accompanying adult; we used information from the Danish Civil Registration System to identify the link from the accompanying adult to the child. Thus, 98.5 percent of the children were identified with the use of the child's civil-registry number or the civil-registry number of the mother or father and the age of the child at vaccination. The remaining 1.5 percent of children were identified on the basis of additional information from the Danish Civil Registration System on other relatives and information on the address at the time of vaccination.

Information about diagnoses of autism was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals, psychiatric departments, and outpatient clinics in Denmark.[22] In our cohort, 93.1 percent of the children were treated only as outpatients, and 6.9 percent were at some point treated as inpatients in a psychiatric department. All diagnoses were based on the *International Classification of Diseases, 10th Revision* (ICD-10), which is similar to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) with regard to autism.[23-26] In Denmark, children are referred to specialists in child psychiatry by general practitioners, schools, and psychologists if autism is suspected. Only specialists in child psychiatry diagnose autism and assign a diagnostic code, and all diagnoses are recorded in the Danish Psychiatric Central Register. We identified all children given a diagnosis of autistic disorder (ICD-10 code F84.0 and DSM-IV code 299.00) or another autistic-spectrum disorder (ICD-10 codes F84.1 through F84.9 and DSM-IV codes 299.10 and 299.80). When a child was given diagnoses of both autistic disorder and one or more other autistic-spectrum disorders, we classified the diagnosis as autistic disorder. Autism is associated with the inherited genetic conditions tuberous sclerosis, Angelman's syndrome, and the fragile X syndrome and with congenital rubella. To maximize the homogeneity of the study population, data for children with these conditions were censored when the diagnosis was made. We obtained information on these conditions from the National Hospital Registry.

We performed an extensive record review for 40 children with autistic disorder (13 percent of all the children with autistic disorder) to validate the diagnosis of autism. A consultant in child psychiatry with expertise in autism examined the medical records. Thirty-seven of the children (92 percent) met the operational criteria for autistic disorder according to a systematic coding scheme developed by the Centers for Disease Control and Prevention for surveillance of autism and used in a prevalence study in Brick Township, New Jersey.[27] The three children who did not meet the criteria for autistic disorder were all classified as having other autistic-spectrum disorders. For two of the children, the diagnosis of autistic disorder was questionable because of profound intellectual impairment. For the third child, we did not have information about the onset of symptoms before the age of three years, which is a prerequisite for the diagnosis of autistic disorder.

We obtained information on birth weight and gestational age from the Danish Medical Birth Registry and the National Hospital Registry.[28,29] Information on potential confounders, including socioeconomic status (as indicated by the employment status of the head of the household) and mother's education was obtained from Statistics Denmark from the time when the child was 15 months of age.

Statistical Analysis

Follow-up for the diagnosis of autistic disorder or another autistic-spectrum disorder began for all children on the day they reached one year of age and continued until the diagnosis of autism or an associated condition (the fragile X syndrome, Angelman's syndrome, tuberous sclerosis, or congenital rubella), emigration, death, or the end of follow-up, on December 31, 1999, whichever occurred first. The incidence-rate ratios for autistic disorder and other autistic-spectrum disorders in the group of vaccinated children, as compared with the unvaccinated group, were examined in a log-linear Poisson regression model with the use of PROC GENMOD (SAS, version 6.12).[30] We treated vaccination as a time-dependent covariate. The children were assigned to the nonvaccinated group until they received the MMR vaccine. From that date, they were followed in the vaccinated group. In additional analyses, the MMR-vaccinated children were grouped according to their age at the time of vaccination, the interval since vaccination, and the calendar period when vaccination was performed.

In reporting the results, we refer to the incidence-rate ratios as relative risks. For all risk estimates, we considered possible confounding by age (1, 2, 3, 4, 5, 6, 7, or 8 to 9 years), sex, calendar period (1992 to 1993, 1994, 1995, 1996, 1997, 1998, or 1999; for other autistic-spectrum disorders, the years 1992, 1993, and 1994 were grouped together), socioeconomic status (six groups), mother's education (five groups), gestational age ($\leq$36, 37 to 41, or $\geq$42 weeks), and birth weight ($\leq$2499, 2500 to 2999, 3000 to 3499, 3500 to 3999, or $\geq$4000 g).

RESULTS

A total of 537,303 children were included in the cohort and followed for a total of 2,129,864 person-years. Follow-up of 5811 children was stopped before December 31, 1999, because of a diagnosis of autistic disorder (in 316 children), other autistic-spectrum disorders (in 422), tuberous sclerosis (in 35), congenital

rubella (in 2), or the fragile X or Angelman's syndrome (in 8), and because of death or emigration in the cases of 5028 children, whose data were censored. For children who received MMR vaccine, there were 1,647,504 person-years of follow-up, and for children who did not receive the vaccine, there were 482,360 person-years of follow-up.

Table 1 shows the distribution of the MMR cohort according to vaccination status, sex, birth weight, gestational age, socioeconomic status, mother's education, and age when autism was diagnosed. The mean age at diagnosis was four years and three months for autistic disorder and five years and three months for other autistic-spectrum disorders. The mean age at the time of the MMR vaccination was 17 months, and 98.5 percent of the vaccinated children were vaccinated before 3 years of age. The proportion of children who were vaccinated was the same among boys and girls (82.0 percent).

Table 2 shows the association between variables related to MMR vaccination and the risk of autism. We calculated the relative risk with adjustment for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status. Overall, there was no increase in the risk of autistic disorder or other autistic-spectrum disorders among vaccinated

TABLE 1. CHARACTERISTICS OF THE 537,303 CHILDREN IN THE DANISH COHORT.

CHARACTERISTIC	VACCINATED CHILDREN (N=440,655)	UNVACCINATED CHILDREN (N=96,648)	P VALUE*
	number (percent)		
Sex			0.55
Male	226,042 (51.3)	49,680 (51.4)	
Female	214,613 (48.7)	46,968 (48.6)	
Birth weight			<0.001
≤2499 g	21,633 (4.9)	5,164 (5.3)	
2500–2999 g	53,874 (12.2)	12,062 (12.5)	
3000–3499 g	135,630 (30.8)	29,262 (30.3)	
3500–3999 g	135,255 (30.7)	29,143 (30.2)	
≥4000 g	66,358 (15.1)	14,563 (15.1)	
Data missing	27,905 (6.3)	6,454 (6.7)	
Gestational age			<0.001
≤36 wk	19,029 (4.3)	3,129 (3.2)	
37–41 wk	272,345 (61.8)	40,609 (42.0)	
≥42 wk	27,349 (6.2)	3,986 (4.1)	
Data missing†	121,932 (27.7)	48,924 (50.6)	
Socioeconomic status‡			<0.001
Manager (very high)	41,367 (9.4)	9,940 (10.3)	
Wage earner (high)	85,772 (19.5)	16,187 (16.7)	
Wage earner (medium)	70,906 (16.1)	13,753 (14.2)	
Wage earner (low)	116,503 (26.4)	26,699 (27.6)	
Wage earner (minimal)	57,408 (13.0)	10,996 (11.4)	
Unemployed	67,841 (15.4)	18,519 (19.2)	
Data missing	858 (0.2)	554 (0.6)	
Mother's education			<0.001
Postgraduate education	26,118 (5.9)	5,856 (6.1)	
College	67,776 (15.4)	14,599 (15.1)	
Vocational training	178,553 (40.5)	34,006 (35.2)	
Secondary school	42,667 (9.7)	10,164 (10.5)	
Primary school	114,768 (26.0)	28,680 (29.7)	
Data missing	10,773 (2.4)	3,343 (3.5)	
Age at diagnosis of autistic disorder			0.87
≤2 yr	48 (0.01)	9 (0.01)	
3–5 yr	187 (0.04)	31 (0.03)	
≥6 yr	34 (0.01)	7 (0.01)	
Age at diagnosis of another autistic-spectrum disorder			0.19
≤2 yr	32 (0.01)	3 (0.003)	
3–5 yr	202 (0.05)	37 (0.04)	
≥6 yr	118 (0.03)	30 (0.03)	

*P values are based on the chi-square test of statistical independence.

†Data were available from the Danish Medical Birth Registry only until December 31, 1996.

‡The employment status of the head of the household was used to indicate socioeconomic status.

TABLE 2. ADJUSTED RELATIVE RISK OF AUTISTIC DISORDER AND OF OTHER AUTISTIC-SPECTRUM DISORDERS IN VACCINATED AND UNVACCINATED CHILDREN.*

VACCINATION	PERSON-YEARS†	AUTISTIC DISORDER		OTHER AUTISTIC-SPECTRUM DISORDERS	
		NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)	NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)
Total	2,129,864	316		422	
Vaccination					
No	482,360	53	1.00	77	1.00
Yes	1,647,504	263	0.92 (0.68–1.24)	345	0.83 (0.65–1.07)
Age at vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
≤14 mo	200,003	38	1.18 (0.78–1.80)	43	0.88 (0.60–1.28)
15–19 mo	1,320,753	195	0.86 (0.63–1.17)	270	0.83 (0.64–1.08)
20–24 mo	69,242	17	1.19 (0.69–2.07)	12	0.62 (0.33–1.13)
25–35 mo	40,935	11	1.20 (0.63–2.31)	15	1.09 (0.63–1.91)
≥36 mo	16,572	2	0.56 (0.14–2.30)	5	0.64 (0.26–1.59)
Interval since vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
<6 mo	212,805	3	0.39 (0.11–1.32)	8	1.18 (0.51–2.75)
6–11 mo	197,931	21	1.38 (0.76–2.51)	4	0.31 (0.10–0.91)
12–17 mo	183,460	22	1.07 (0.59–1.95)	16	0.92 (0.47–1.80)
18–23 mo	168,045	31	0.86 (0.52–1.41)	16	0.47 (0.26–0.86)
24–29 mo	154,290	42	0.99 (0.61–1.58)	32	0.77 (0.46–1.27)
30–35 mo	139,258	33	0.86 (0.54–1.38)	27	0.69 (0.43–1.11)
36–59 mo	406,320	90	0.99 (0.66–1.50)	158	1.05 (0.77–1.45)
≥60 mo	185,396	21	0.67 (0.34–1.33)	84	0.75 (0.51–1.09)
Date of vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
1991–1992	248,646	31	1.00 (0.59–1.70)	61	0.75 (0.51–1.09)
1993–1994	659,152	81	0.73 (0.50–1.06)	146	0.74 (0.56–0.99)
1995–1996	475,990	96	0.91 (0.63–1.30)	116	1.13 (0.81–1.56)
1997–1999	263,716	55	1.35 (0.84–2.17)	22	0.71 (0.40–1.24)

*The relative risk was adjusted for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status of the family. The reference group was the group of children who were not vaccinated. The distribution of cases of autistic disorder or other autistic-spectrum disorders according to vaccination status differs from that in Table 1 because, in this analysis, children who were vaccinated after the disorder had been diagnosed were classified according to their vaccination status at the time of the diagnosis (i.e., as unvaccinated). CI denotes confidence interval.

†Because of rounding, the numbers of person-years do not necessarily sum to the total shown.

children as compared with unvaccinated children (adjusted relative risk of autistic disorder, 0.92; 95 percent confidence interval, 0.68 to 1.24; adjusted relative risk of other autistic-spectrum disorders, 0.83; 95 percent confidence interval, 0.65 to 1.07). Furthermore, we found no association between the development of autistic disorder and the age at vaccination ($P=0.23$), the interval since vaccination ($P=0.42$), or the calendar period at the time of vaccination ($P=0.06$).

Adjustment for potential confounders with the exception of age resulted in similar estimates of risk. Changing the start of follow-up for autistic disorder and other autistic-spectrum disorders to the date of birth or 16 months of age had little effect on the estimates (data not shown). Furthermore, including children with the fragile X syndrome, tuberous sclerosis, congenital rubella, or Angelman's syndrome in the analysis did not change the estimates (data not shown).

DISCUSSION

This study provides three strong arguments against a causal relation between MMR vaccination and autism. First, the risk of autism was similar in vaccinated and unvaccinated children, in both age-adjusted and fully adjusted analyses. Second, there was no temporal clustering of cases of autism at any time after immunization. Third, neither autistic disorder nor other autistic-spectrum disorders were associated with MMR vaccination. Furthermore, the results were derived from a nationwide cohort study with nearly complete follow-up data.

All previous studies of an association between autism and MMR vaccination have been case series,[1,14,15] ecologic studies,[11,12] or cross-sectional studies,[10,13] and the majority have not used optimal data for risk assessment. In a well-conducted, cross-sectional prevalence study, Taylor and colleagues[10] found that there was no sharp increase in the prevalence of autism after the in-

troduction of the MMR vaccine. However, it could be argued that a more gradual increase would be expected, since autism is characterized by an insidious onset and a delay in diagnosis. A case-series study by Peltola et al.[15] also provides evidence against a causal connection.

One of the main reasons for public concern has been that the widespread use of the MMR vaccine in some regions appeared to coincide with an increase in the incidence of autism. However, this is not a uniform finding. In Denmark, the prevalence of autism (according to the criteria of the *International Classification of Diseases, 8th Revision*) was less than 2.0 cases per 10,000 children between the ages of five and nine years in the 1980s and the beginning of the 1990s. Since then, the rates have increased in all age groups except for children younger than two years of age, and in 2000, the prevalence of autism (according to the ICD-10 criteria) was higher than 10.0 cases per 10,000 children five to nine years of age (unpublished data). Thus, the increase in autism both in California[5] and in Denmark occurred well after the introduction of the MMR vaccine.

Our study was based on individual reports of vaccination and diagnoses of autism in a well-defined geographic area. The exposure data were collected prospectively, independently of parental recall and before the diagnosis of autism. Furthermore, the diagnosis was recorded independently of the recording of MMR vaccination. Thus, there was little possibility of differential misclassification of exposure or outcome measures. Furthermore, our analysis was based on complete follow-up data.

We assume that the data on MMR vaccination are almost complete, since general practitioners in Denmark are reimbursed only after reporting immunization data to the National Board of Health. We had an unvaccinated reference group with almost 500,000 person-years of follow-up, even though the study was numerically imbalanced in favor of the vaccinated group. The power of the study is reflected in the narrow 95 percent confidence intervals.

We had no information on the presence or absence of a family history of autism, which could explain our negative findings only if families with a history of autism avoided MMR vaccination. If so, we would expect to have found high relative risks at the beginning of the study period, before the hypothetical link between vaccination and autism was publicized. This was not the case. We had no information on whether the children with autism had regression, and thus we could not perform a subgroup analysis. However, the fact that the overall relative risk of autism or an autistic-spectrum disorder was less than 1.0 does not support the possibility of a subgroup of vulnerable children.

The Danish vaccination program recommends that children receive the MMR vaccine at 15 months of age and provides the vaccination free of charge. Among the children in our cohort who were born in 1995, the rate of MMR vaccination was lower than the rate of vaccination with the first *Haemophilus influenzae* type B vaccine (86.9 percent vs. 97.0 percent). However, the rate of MMR vaccination in our study was similar to that in the United States (87.6 percent in 1995) and Belgium (83.0 percent in 1997).[31,32] Nevertheless, the main concern is the comparability of vaccinated and nonvaccinated children in relation to the end point under study. In all analyses, when risk estimates were calculated, we controlled for possible confounders (age, sex, calendar period, socioeconomic status, mother's education, gestational age, and birth weight). Except for age, none of these possible confounders changed the estimates. The confounding by age was a function of the time available for follow-up, since much of the follow-up for the unvaccinated group involved young children, in whom autism is often undiagnosed.

We assessed the validity of the diagnosis of autistic disorder in a subgroup of children and found it to be high. This was to be expected, since only specialists in child and adolescent psychiatry are authorized to code the diagnosis of autism in the Danish Psychiatric Central Register. All schools have access to health care personnel as well as psychologists. Because of the comprehensive health care surveillance for children in Denmark, all severe cases of autism are likely to be diagnosed and reported to the registry at some point. Reporting of the other autistic-spectrum disorders is less complete than that for autistic disorder, and some diagnoses are almost certainly missed. However, it is unlikely that this misclassification would be associated with vaccination status. It is very difficult to determine the onset of autism, and many cases are probably due to prenatal factors. Our records did not contain information on when the first autistic symptoms were noted, and we could not adjust for a differential delay in the diagnosis. Again, it is highly unlikely that a delayed diagnosis was associated with MMR vaccination in this study.

There are few published data on the incidence of autism, but the prevalence rates reported in the literature vary widely, from 1.2 cases per 10,000 (according to the criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*) to 30.8 per 10,000 (according to the ICD-10 criteria).[33,34] The prevalence rates among eight-year-old children in our cohort were 7.7 per 10,000 for autistic disorder and 22.2 per 10,000 for other autistic-spectrum disorders. These rates are similar to the prevalence rates of 5.4 per 10,000 for autistic disorder and 16.3 per 10,000 for other autistic-spectrum disorders in a cohort of 325,347 French children (ICD-10 criteria), reported

by Fombonne et al.,[35] and the rate of 11 per 10,000 for autistic disorder in a cohort of U.S. children (DSM-IV criteria), reported by Croen and colleagues.[36] The DSM-IV classification system used in the United States and the ICD-10 classification system used in many European countries are almost identical with regard to the classification of autistic disorder.[23-26] In our validity substudy, we found that 93 percent of cases diagnosed according to the ICD-10 criteria met the DSM-IV operational criteria for the diagnosis of autistic disorder.

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ORIGINAL ARTICLE

A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism

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Measles, Mumps, and Rubella Vaccination and Autism

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Article

To the Editor:

The publication of a controlled epidemiologic study on the measles, mumps, and rubella (MMR) vaccine and autism (Nov. 7 issue)[1] represents a major advance. The great volume of material circulating on the Internet about a possible link between the MMR vaccine and autism cannot undermine the strength of the design. However, the study has some methodologic problems. A review of the clinical records for only 40 of the 316 children with autistic disorder is inadequate. That was clear in another review, which focused on 493 self-selected British children with autistic syndrome[2]: without a multidisciplinary review of lifetime records, important errors would have been unavoidable. Although it would be difficult, with the use of clinical criteria one could identify subgroups among most of the children, notably subgroups with regression.

The power of the current study[1] was high (80 percent to detect a relative risk of 1.5) but misleading. Let us assume hypothetically that there is a vulnerability to MMR-induced disease in 10 percent of the children with autism. We can assume further that 80 percent of the overall group with autism and 95 percent of the subgroup with vulnerability have been vaccinated. In a nested, case–control design within the Danish cohorts, the odds ratio for MMR in the subgroup would be 4.17; for all the children with autism combined, the odds ratio would be 0.97, masking the association in a small subgroup. Yet, in a conservative estimate, 10 percent would represent 50,000 children in the United States, at a yearly burden of $1.25 billion. I hope this possibility can be ruled out.

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2 References

To the Editor:

The admirable attempt by Madsen et al. to evaluate a possible association between the MMR vaccine and autism has multiple flaws that compound the bias toward a finding of no association. First, the use of person-years instead of persons in the analysis magnifies the weight of the early cases (when the prevalence of autism was relatively low) and minimizes the weight of the later cases (when the prevalence was five times that in the early period). Second, the mean ages at diagnosis were 51 months for autism and 63 months for other autistic-spectrum disorders. A child born early in the study period had a higher likelihood of receiving a

diagnosis than a child born later in the study period. Finally, children in the unvaccinated group underwent a mean of 5.0 years of follow-up (482,360 person-years for 96,648 persons), as compared with 3.7 years in the vaccinated group (1,647,504 person-years for 440,655 persons). This discrepancy also reduced the likelihood that autism would be detected in a vaccinated child as compared with an unvaccinated child.

The authors overstate their conclusion in the abstract by saying, "This study provides strong evidence against the hypothesis that MMR vaccination causes autism." Even if the study did not suffer from these flaws, the strongest defensible conclusion would be that the study did not detect an association between MMR and autism.

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To the Editor:

Inadequate epidemiologic studies, in contrast with laboratory studies,[1,2] have not found an association between MMR vaccination and autism. Madsen et al. fail to disaggregate the relevant subgroup from the overall population with autism.

My own hypothesis, untested at the population level, involves a subgroup of children with regressive autism associated with gastrointestinal inflammation and apparently type 2 helper T cell (Th2)–skewed mucosal and systemic immunity. In 1999 a colleague and I wrote, "The newborn tends towards a Th2 response to pathogens and gradually shifts towards a Th1 [type 1 helper T cell] response with age. If this transition does not take place appropriately, the infant is likely to be at greater risk of mounting aberrant immune responses in later life."[3] In considering children at risk, cofactors that may interfere with a Th2-to-Th1 transition in infants require examination. Mercury exposure alters the susceptibility to infection. Murine susceptibility to infection with *Leishmania major* reflects a genetically restricted Th2 response. In resistant animals (with a Th1 response to *L. major*), a Th2-mediated autoimmune syndrome develops, and the animals are unable to clear the infection after exposure to mercury.[4]

Hypothesis testing at the population level must adjust for cofactors that might influence the response to MMR — an impossible task, perhaps, given infants' increasing exposure to mercury in vaccines. Answers may be found only in detailed examination of each child.

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4 References

To the Editor:

Suspicions about vaccine safety, discussed by Campion in his Perspective,[1] are contributing to a growing measles crisis in Japan. In 1995, the government enacted a law making immunizations optional. Because of parents' fear of rare vaccine-related encephalopathic complications, mounting medicolegal concern on the part of physicians, and limited intervention by the government, compliance with measles vaccination is poor. Cases of measles in Japan now number more than 100,000 per year,[2] with an estimated 50 to 100 deaths annually. The effects of this problem are crossing borders. Of the 86 total cases of measles in the United States in 2000, 62 percent were importation-associated. Twenty-six of the 86 cases (30 percent) were imported. Japan contributed the largest number of cases from a single country (7 of the 26 imported cases).[3]

Measles has the potential to cause substantial morbidity and mortality, not only in the developing world but also in the developed world. Public health authorities have an important role in objectively educating both physicians and the public about vaccines, in supporting physicians in vaccinating children, and in improving vaccination programs. A coordinated global effort will be critical for preventing the spread of vaccine-preventable diseases such as measles.

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3 References

Dr. Madsen replies: Whether it is possible to perform hypothesis testing at all at any level is a matter for debate elsewhere. A hypothesis can, however, be subject to critical evaluation in population-based studies, such as ours. We found no corroboration for the hypothesis that MMR vaccination causes autism.

Dr. Wakefield argues that we should have controlled for mercury exposure from vaccines. However, mercury — or more precisely, the vaccine preservative thimerosal that contains ethyl mercury — has not been used in Danish vaccines since 1992 and thus was not a confounder in the study.

Dr. Spitzer will probably agree that our task is to examine (not to prove) proposed causal links between exposure and diseases. We cannot rule out the possibility that at least one child would not have become autistic if he or she had not been vaccinated, and that point alone may be sufficient for stating causality. Unfortunately, we cannot subject this assumption to a critical test unless it is better specified. We can say that if this causal link exists, it is not frequent. We can say that MMR vaccination is not the explanation for an increasing incidence in autism, if such an increasing incidence exists. We can say that MMR vaccination is not one of the common causes of autism. But we cannot prove anything, especially not when it comes to null hypotheses.

All effect measures have a set of confidence limits that vary in width and credibility according to the size and quality of the study. We do not claim to have proven that MMR vaccination can never cause autism. We can state only that we find nothing in our data to support the hypothesis that MMR causes autism. We cannot rule out the existence of a susceptible subgroup with an increased risk of autism if vaccinated, but such a subgroup must be small. Even if such a hypothetical subgroup exists, its members may be better off receiving the vaccine, when all the risks and benefits are taken into consideration.

We are in the process of evaluating diagnoses for all the cases of autism in the cohort, and so far, the estimates of validity have not changed. This was to be expected, since only specialists in child and adolescent psychiatry were authorized to diagnose autism.

With regard to Dr. Mullins's comments: it is important to note that we did adjust for both age and calendar period in the analysis. Vaccination was treated as a time-dependent covariate, and the vaccinated children contributed risk time in the unvaccinated group until they were vaccinated. Thus, calculating the mean years of follow-up the way Dr. Mullins suggests is not possible.

Kreesten Meldgaard Madsen, M.D.
Danish Epidemiology Science Center, DK-8000 Aarhus C, Denmark
kmm@dadlnet.dk

Dr. Campion replies: The experience that Drs. Noble and Miyasaka describe is sobering. People want more independence and more control over all health care decisions. However, if the rate of childhood vaccination declines substantially, the result will be needless harm to young children. It is particularly sad when fears about vaccination begin to spread because of statements in the scientific literature that are hypothetical and unproven. The large, careful study by Madsen et al. found absolutely no evidence to support the hypothesis that MMR vaccination is responsible for the development of autism.

Edward W. Campion, M.D.

Exhibit 18

Wojcik, Joanne (CDC/CCHP/NCBDDD)

From: Wojcik, Joanne (CDC/CCHP/NCBDDD)
Sent: Thursday, December 10, 2009 10:46 AM
To: (DK) Kjaergaard, Soren; (DK) Obel, Carsten ; (DK) Parner, Eric; Boyle, Coleen (CDC/CCHP/NCBDDD); Rice, Catherine (CDC/CCHP/NCBDDD); Schendel, Diana (CDC/CCHP/NCBDDD); Thorsen, Poul; Van Naarden-Braun, Kim (CDC/CCHP/NCBDDD); Vogt, Robert (CDC/CCEHIP/NCEH); Wojcik, Joanne (CDC/CCHP/NCBDDD); Yeargin-Allsopp, Marshalyn (CDC/CCHP/NCBDDD)
Subject: Denmark / CDC Autism/CP Call - Monday, December 14, 2009 8-9am Eastern US

Attachments: [Untitled].pdf

[Untitled].pdf (2 MB)

Please see the call notes from our November 30th call. We will review the action items from our last call and continue w/new discussion topics. Looking forward to talking with you on Monday.

Soren/Carsten - Could you please be sure that David Hougaard receives this info as appropriate?

Please let me know if you have any questions. tx jw

When: Monday, December 14, 2009 8:00 AM-9:00 AM (GMT-05:00) Eastern Time (US & Canada).
Where: Via teleconference (Eastern Standard Time)

~~*~*~*~*~*~*~*~*

Dear colleagues,

Thank you again for your participation in the CDC-Denmark CP/autism workgroup; the call-in information is below.

Toll Free/Freephone Number : AUSTRALIA (b)(6)
DENMAR (b)(6)
SPAIN
SWEDEN
USA

Leader Passcode : (b)(6)
Participant Passcode :

Future Calls, 8am-9am Eastern US

January 11, 25
February 8, 22
March 8, 22

Joanne Wojcik
Public Health Analyst
Developmental Disabilities Branch
CDC, National Center on Birth Defects and Developmental Disabilities Physical Address/Private Courier:

1825 Century Boulevard, Atlanta, GA 30345 USPS Mail to: 1600 Clifton Road, M/S E-86, Atlanta, GA 30333
Phone: (404) 498-3848 Fax: (404) 498-3550
Email: jcw6@cdc.gov

Denmark Grantee Autism/CP Call
November 30, 2009
8 am Eastern/2pm Denmark

12/14

Call Participants

CDC:
- Coleen Boyle, Director, Division of Birth Defects and Developmental Disabilities (DBDDD), CDC
- Marshalyn Yeargin-Allsopp, Medical Epidemiologist, Chief, Developmental Disabilities Branch (DDB)
- Diana Schendel, Epidemiology Team Lead, DDB
- Kim Van Naarden Braun, Surveillance Team Lead, DDB
- Joanne Wojcik, Public Health Analyst, DDB

Denmark, Aarhus University:
- Søren Kjaergaard, Head of Institute, Principal Investigator on Cooperative Agreement
- Eric Parner, Assoc. Prof. at Dept of Biostatistics
- Carsten Obel, Assoc. Prof. at Dept of General Medicine
- Nils Anderson, Technical Coordinator

Review of Action Items from the last call (some updates provided in Carsten/Erik's document).

Action List (consolidated listing from the November 10, 2009 call):

1. Søren and Carsten to provide an SSI update on our next call.

Comments: Update provided below by Carsten and Eric. Søren will ensure that David Hougaard is included in future calls.

2. Poul is requested to provide Aarhus University a copy of all permissions in his files ASAP.

Comments: Email note from Poul 11/30/09 – "The approvals for the studies, which I have on hand, have been revealed to Carsten and Erik previously and can be found on http://www.datatilsynet.dk/english/. As I have stated before to Carsten and Erik, I have not been able to locate the ethical approval for the autism pilot study. I recommend that new approvals are requested just as stated in the notes from the last conference call."

3. Carsten and Eric will be responsible for securing all appropriate permissions and data management across the project.

Comments: Carsten and Eric provided an update below.

4. **Marshalyn will contact Peter Uldall regarding the CP registers.**

Comments: Marshalyn attempting to contact Peter.

5. **Søren, Erik and Carsten will also connect with Peter Uldall regarding the continuation for 2009 and the completion of the data collection (CP register).**

Comments: Denmark folks also attempting to connect with Peter.

6. **Aarhus University to provide an update on a future call regarding the DNBC Based Studies.**

<u>Action List/ACTION ITEM Items (consolidated listing from today's call (November 30, 2009)):</u>

1. **Diana will review the referenced Buttenschon paper (reference 1) and get back to the group.**

2. **Carsten will provide the Permission Committee quarterly meeting schedule for the next call.**

3. **Carsten will provide the workgroup a description of the Denmark permission process in English.**

4. **Søren will review and provide an update re the abstraction. He had thought it was ongoing.**

5. **Joanne to reattach Diana's update sheet to the next minutes.**

Comments: Joanne emailed document to group 11/30/09.

6. **Søren will send David Hougaard an invite for future calls. If the day/time does not work with David's schedule another call time will need to be identified.**

It was confirmed that the below day/time works for the call participants.
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January 11, 25
February 8, 22
March 8, 22

Carsten and Eric provided the below short report for today's call (*in italics*).

Overall progress

CP registry

We have had meetings with Peter Uldall from the CP registry and the abstraction team (Gija Rackauskaite and Annette Bang Rasmussen) to arrange for completion of the CP registry of cases in western Denmark for birth year 1995-2003. The abstraction to the CP registry is expected to be finalized by February 1th 2010. Further, the medical birth record abstraction is expected to be finalized by April 1th 2010. A new agreement of collaboration between Institute of Public Health, AU, and the CP registry is being set up.

Q- docs./Danish National Birth Cohort (DNBC) Based Studies

A total 162 children with CP were selected to have their medical record abstracted, of which 127 have been abstracted. A total of 1330 controls were selected of which 1203 have been abstracted.

Biomarker panel

We had a meeting with David Hougaard. He is willing to discuss new projects using the inflammatory panel and say that we (CDC/Aarhus University) if we have specific ideas have the first right to use the panel for these purposes. He and his people also use the panel for other purposes that he believes do not interfere with our areas of interest. He thinks that testing 1000 persons costs about $20,000. He estimated that CDC/Aarhus University has financed on third of the cost of developing the panel. He is ready to start developing the new panel but awaits the financing from CDC.

Comments: Marshalyn is unclear about "developing the new panels". Per Carsten, he met with David Hougaard and they were discussing the possibility of using the already developed panel. David Hougaard is interested in new projects since the panels are now developed. It was mentioned that if another group of research subjects were to be used there would need to be another clearance from the Ethical Review Panel. Marshalyn asked Diana if there are any new questions that could be answered based on the inflammatory biomarker panel? Diana stated there could be some additional analyses completed.

Coleen thought that David Hougaard was working on the new panel and he had an additional year of work to complete this activity. Diana mentioned the new panel is an autism panel. Carsten will re-review his notes (may not have captured information appropriately). Carsten mentioned the inflammatory panel is completed and quite inexpensive to now run on samples. Søren believes David Hougaard has started on the second panel. Coleen would also like Søren to review the budget for FY 2009.

Permissions

The CP registry data

The eastern Denmark registry is a national register and the permission for western Denmark should be covered by this permission (originally given to Peter Uldall)

Bio- and genetic markers and CP

A permission from Jes Vestergaard from the Ethical Committee is currently being transferred to David Hougaard and extended to include genetics. A new permission from the Data Protection Agency is also needed. Then all permissions for bio- and genetic marker and CP are in place.

Comments: Per Carsten these permissions will be moved to David Houggaard. It should not take that long to get the permission moved; should take approximately 1-2 months.

Bio- and genetic markers and autism

We have not been able to find a permission from ethical committee that covers both bio- and genetic markers and autism. As far as we understand only one paper has been published using these data[1] and Diana will soon be submiting another. Apart from the letter from the EC in our region (attached) we have not been able to locate the permission for abstraction of the psychiatric records, and it is likely that it does not exist. We are currently working on an application for bio- and genetic markers to the Ethical Committee (EC) and Data Protection Agency that will cover both CP and autism.

Comments: Carsten believes one paper has been published using this dataset. Appears there is no permission to conduct this activity. They will apply for a new permission and mention that something was completed without permission. Diana mentioned that there was more than one paper completed. Carsten asked Diana to provide any additional papers published under this activity. Diana does not believe there were any papers published. Diana is not sure if the below paper was a part of this dataset.

ACTION ITEM: Diana will review the referenced Buttenschon paper (reference 1) and get back to the group.

Buttenschon HN, Lauritsen MB, El DA et al. A population-based association study of glutamate decarboxylase 1 as a candidate gene for autism. J Neural Transm 2009;116(3):381-388.

Carsten wants to be sure that the permission is received prior to the publication of Diana's inflamatory biomarkers paper. Søren had met previously with David Hougaard months ago and he referred to Poul with the needed permissions.

Diana mentioned individual permission was received for the CP biobank data. For the autism dataset Diana remembers individual permission was not required of each participant. Individual permissions were received in the case control study.
The Danish Agency has permission reviews four times a year. They are attempting to keep these activities on track to get permissions as soon as possible.
Per Søren there should be no challenge to get it cleared. Coleen asked if we could continue the analyses? Coleen asked if there is a record of permission sought in the past? Eric asked the ethical committee if there were any previous permissions; none were found. Per Diana at the time the Danish Data Protection Agency was only required. No additional permission had been needed. Per Carsten he believes permission should have been sought previously by the ethical committee. Per Eric he has seen a similar application since the 1990's.

Carsten and Eric are attempting to gather all of the various permissions into one application package. Per Marshalyn it appears the rules are in the U.S. where you can access some data without individual consent. Carsten and Eric will be preparing the permissions application to the committee. Autism, CP and ADHD will be combined into one permission.

ACTION ITEM: Carsten will provide the Permission Committee quarterly meeting schedule for the next call.

Diana offered to provide additional scientific content information. They will provide Diana and Marshalyn with a copy of the protocol.

Autism database

One paper has been published describing these data[2] and another describing the use of patient files[3]. At the time the psychiatric records were abstracted permission from the Danish National Board of Health (DNBH) should have been applied for. However, there was at that time confusion among scientists if the permission should come from the EC or DNBH or if it was really necessary. In fact EC gave permissions in this period. Although it probably is possible to get such a permission from DNBH that covers future projects, it seem like it will be difficult - probably impossible - to get a permission that covers ongoing or finalized project (back in time). We believe, however, that we have found a possible solution to this problem by extending a related permission from Ethical Committee that was given to a colleague at our institute (Rikke Maimburg). This project was approved in 2000 (title ' Obstetric factors and autism', the permission that covers one of the papers Diana is in charge of) and used mother's obstetric files. It is hoped that it is possible to extend this project to include psychiatric patient files for validating the Psychiatric Register diagnosis.

Comments: Carsten stated there should have been an application to the National Board of Health; not from the Ethical Committee. It is difficult to get the permission back in time. Data have been used for a couple of studies. The medical records mentioned in the paper were referring to the validation study. According to the law the National Board of

Health should have been asked. Per Diana she believes the permissions were in place for the below paper. They had to get permission from each hospital and doctor to review the records. Diana does not recall the specifics for the administrative permissions for the below paper. Diana mentioned that at the time the thought was to establish an autism registry similar to the CP registry.

Lauritsen MB, Jorgensen M, Madsen KM et al. Validity of Childhood Autism in the Danish Psychiatric Central Register: Findings from a Cohort Sample Born 1990-1999. J Autism Dev Disord 2009.

Madsen KM, Hviid A, Vestergaard M et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002;347(19):1477-1482.

Coleen suggested we outline specific projects that we are seeking permission to provide more clarity. Marshalyn agreed Denmark is working on the best strategy to identify appropriate permissions (in retrospect). Per Søren working with the National Board of Health is a little more difficult to work through.

Coleen believes CDC has to inform the CDC IRB office to alert them of the issue of permissions not available. Coleen asked for additional clarification regarding the Denmark Permission process.

ACTION ITEM: Carsten will provide the workgroup a description of the Denmark Permission process in English.

Diana mentioned that the Ethical Committee is similar to the U.S. IRB Board. Per Marshalyn an approach needs to be decided before a timeline can be finalized. Marshalyn believes this permission may be more complicated.

Danish National Birth Cohort (DNBC) Based Studies

Permission should be ok according the DNBC secretay, since the participants have given consent to participate in on the DNBC and thus the use of data from the health system.

Comments:

Carsten noted that the DNBC has signed individual permissions for participation in studies. Coleen suggested to Marshalyn that CDC scientists talk in house regarding CP analyses before further discussion on a future Denmark conference call. Diana agrees with this plan.

Søren mentioned the Citrix Server is working. The data will be placed on the server along with variable descriptions. This will allow all of the data to reside in one place. Will then discuss analyses and data sharing.

Coleen asked about the Quality Control for the CP Medical Record Abstraction. Coleen believes Lars Ostergard was going to setup the QC. ACTION ITEM: Søren will get an update from Lars.

ACTION ITEM: Søren will review and provide an update re the abstraction. He had thought it was ongoing.

ACTION ITEM: Joanne to reattach Diana's update sheet to the next minutes.
Comment: Joanne emailed Diana's update sheet to all 11/30/09.

Marshalyn would like to be sure that the David Hougaard is available for future calls.

ACTION ITEM: Søren will send David Hougaard an invite for future calls. If the day/time does not work with David's schedule another call time will need to be identified.

Next Call:

When: Monday, December 14, 2009 8:00 AM-9:00 AM (GMT-05:00) Eastern Time (US & Canada).
Where: Via teleconference (Eastern Standard Time)

Toll Free/Freephone Number :
AUSTRALI (b)(6)
DENMARK
SPAIN (b)(6)
SWEDEN (b)(6)
USA (b)(6)

Leader Passcode :
Participant Passcode : (b)(6)

Reference List

1. Buttenschon HN, Lauritsen MB, El DA et al. A population-based association study of glutamate decarboxylase 1 as a candidate gene for autism. J Neural Transm 2009;116(3):381-388.

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11/30/09

Wojcik, Joanne (CDC/CCHP/NCBDDD)

From: Wojcik, Joanne (CDC/CCHP/NCBDDD)
Sent: Monday, November 30, 2009 3:15 PM
To: 'SK@FOLKESUNDHED.AU.DK'; 'Carsten Obel'
Cc: Yeargin-Allsopp, Marshalyn (CDC/CCHP/NCBDDD); Wojcik, Joanne (CDC/CCHP/NCBDDD)
Subject: Denmark 2009-11-30 Autis-CP Call.doc

Attachments: Denmark 2009-11-30 Autis-CP Call.doc

Denmark
09-11-30 Autis-CP C

Good Day Soren and Carsten: I've provided a draft of today's notes/to do lists as an attachment to this email. I would appreciate it very much if maybe Carsten could provide a review from Denmark's perspective and revise as appropriate. I'll then be sure to get CDC's review before I send out as final. Carsten your notes w/Eric were very beneficial to provide a solid starting point for today's discussions; thank you so much for sending prior to today's call.

If possible I'd like to get these notes out by the end of the week.

tx much

jw

Denmark Grantee Autism/CP Call
November 30, 2009
8 am Eastern/2pm Denmark

Call Participants

CDC:
Coleen Boyle, Director, Division of Birth Defects and Developmental Disabilities (DBDDD), CDC
Marshalyn Yeargin-Allsopp, Medical Epidemiologist, Chief, Developmental Disabilities Branch (DDB)
Diana Schendel, Epidemiology Team Lead, DDB
Kim Van Naarden Braun, Surveillance Team Lead, DDB
Joanne Wojcik, Public Health Analyst, DDB

Denmark, Aarhus University:
Søren Kjaergaard, Head of Institute, Principal Investigator on Cooperative Agreement
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Nils Anderson, Technical Coordinator

Review of Action Items from the last call (some updates provided in Carsten/Erik's document).

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Comments: Update provided below by Carsten and Eric. Søren will ensure that David Hougaard is included in future calls.

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Comments: Email note from Poul 11/30/09 – quote - The approvals for the studies, which I have on hand, have been revealed to Carsten and Erik previously and can be found on http://www.datatilsynet.dk/english/. As I have stated before to Carsten and Erik, I have not been able to locate the ethical approval for the autism pilot study. I recommend that new approvals are requested just as stated in the notes from the last conference call, unquote.

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Søren mentioned the Citrix Server is working. The data will be placed on the server along with variable descriptions. This will allow all of the data to reside in one place. Will then discuss analyses and data sharing.

Coleen asked about the Quality Control for the CP Medical Record Abstraction. Coleen believes Lars Ostergard was going to setup the QC. TO DO: Søren will get an update from Lars.

TO DO: Søren will review and provide an update re the abstraction. He had thought it was ongoing.

- **TO DO:** Joanne to reattach Diana's update sheet to the next minutes. **Comment:** Joanne emailed Diana's update sheet to all 11/30/09.

Marshalyn would like to be sure that the David Hougaard is available for future calls. TO DO: Søren will send David Hougaard an invite for future calls. If the day/time does not work with David's schedule another call time will need to be identified.

Next Call:

When: Monday, December 14, 2009 8:00 AM-9:00 AM (GMT-05:00) Eastern Time (US & Canada).
Where: Via teleconference (Eastern Standard Time)

Toll Free/Freephone Number :
AUSTRALIA (b)(6)
DENMARK (b)(6)
SPAIN (b)(6)
SWEDEN (b)(6)
USA (b)(6)

Leader Passcode : (b)(6)
Participant Passcode :

Reference List

1. Buttenschon HN, Lauritsen MB, El DA et al. A population-based association study of glutamate decarboxylase 1 as a candidate gene for autism. J Neural Transm 2009;116(3):381-388.

2. Lauritsen MB, Jorgensen M, Madsen KM et al. Validity of Childhood Autism in the Danish Psychiatric Central Register: Findings from a Cohort Sample Born 1990-1999. J Autism Dev Disord 2009.

3. Madsen KM, Hviid A, Vestergaard M et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002;347(19):1477-1482.

Short report for the telephone meeting 30th November 2009

Overall progress

CP registry

We have had meetings with Peter Uldall from the CP registry and the abstraction team (Gija Rackauskaite and Annette Bang Rasmussen) to arrange for completion of the CP registry of cases in western Denmark for birth year 1995-2003. The abstraction to the CP registry is expected to be finalized by February 1th 2010. Further, the medical birth record abstraction is expected to be finalized by April 1th 2010. A new aggrement of collaboration between Institute of Public Health, AU, and the CP registry is being set up.

Q- docs./Danish National Birth Cohort (DNBC) Based Studies

A total 162 children with CP were selected to have their medical record abstracted, of which 127 have been abstracted. A total of 1330 controls were selected of which 1203 have been abstracted.

Biomarker panel

We had a meeting with David Hougaard. He is willing to discuss new projects using the inflammatory panel and say that we (CDC/Aarhus University) if we have specific ideas have the first right to use the panel for these purposes. He and his people also use the panel for other purposes that he believes do not interfere with our areas of interest. He think that testing 1000 persons cost about 20 000 $. He estimated that CDC/Aarhus University has financed on third of the cost of developing the panel. He is ready to start developing the new panel but awaits the financing from CDC.

Permissions

The CP registry data

The eastern Denmark registry is a national register and the permission for western Denmark should be covered by this permission (originally given to Peter Uldall)

Bio- and genetic markers and CP

A permission from Jes Vestergaard from the Ethical Committee is currently been transferred to David Hougaard and extended to include genetics. A new permission from the Data Protection Agency is also needed. Then all permissions for bio- and genetic marker and CP are in place.

Bio- and genetic markers and autism

We have not been able to find a permission from ethical committee that covers both bio- and genetic markers and autism. As far as we understand only one paper has been published using these data[1] and Diana will seen submit another. Apart from the letter from the EC in our region (attached) we have not been able to locate the permission for abstraction of the psychiatric records, and it is likely that it does not exist. We are currently working on an application for bio- and genetic markers to the Ethical Committee (EC) and Data Protection Agency that will cover both CP and autism.

Autism database

One paper has been published describing these data[2] and another describing the use of patient files[3]. At the time the psychiatric records were abstracted permission from the Danish National Board of Health (DNBH) should have been applied for. However, there was at that time confusion among scientists if the permission should come from the EC or DNBH or if it was really necessary. In fact EC gave permissions in this period. Although it probably is possible to get such a permission from DNBH that covers future projects, it seem like it will be difficult - probably impossible - to get a permission that covers ongoing or finalized project (back in time). We believe, however, that we have found a possible solution to this problem by extending a related permission from Ethical Committee that was given to a colleague at our institute (Rikke Maimburg). This project was approved in 2000 (title ' Obstetric factors and autism', the permission that covers one of the papers Diana is in charge of) and used mother's obstetric files. It hope it is possible to extend this project to include psychiatric patient files for validating the Psychiatric Register diagnosis.

Danish National Birth Cohort (DNBC) Based Studies

Permission should be ok according the DNBC secretay, since the participants have given consent to participate in on the DNBC and thus the use of data from the health system.

Erik Parner and Carsten Obel

Reference List

1. Buttenschon HN, Lauritsen MB, El DA et al. A population-based association study of glutamate decarboxylase 1 as a candidate gene for autism. J Neural Transm 2009;116(3):381-388.

2. Lauritsen MB, Jorgensen M, Madsen KM et al. Validity of Childhood Autism in the Danish Psychiatric Central Register: Findings from a Cohort Sample Born 1990-1999. J Autism Dev Disord 2009.

3. Madsen KM, Hviid A, Vestergaard M et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002;347(19):1477-1482.

Wojcik, Joanne (CDC/CCHP/NCBDDD)

From: Erik Parner [PARNER@BIOSTAT.AU.DK]
Sent: Friday, November 27, 2009 8:21 AM
To: Wojcik, Joanne (CDC/CCHP/NCBDDD)
Cc: Carsten Obel
Subject: RE: Denmark Call Notes - November 30, 2009
Attachments: Progress report.doc

Dear Joanne,

Carsten Obel and I have made a brief report of our activities for the conference call Monday, November 30. Would be kind to distribute the report to all the relevant persons?

Kind regards,

Erik Parner

11/10/09

Denmark Grantee Autism/CP Call
November 10, 2009
8 am Eastern/2pm Denmark

Call Participants

CDC:
Coleen Boyle, Director, Division of Birth Defects and Developmental Disabilities (DBDDD), CDC
Marshalyn Yeargin-Allsopp, Medical Epidemiologist, Chief, Developmental Disabilities Branch (DDB)
Diana Schendel, Epidemiology Team Lead, DDB
Kim Van Naarden Braun, Surveillance Team Lead, DDB
Cathy Rice, Epidemiologist, Surveillance Team, DDB
Joanne Wojcik, Public Health Analyst, DDB
Bob Vogt, National Center for Environmental Health (NCEH) Laboratory (could not attend this call; but is interested)

Denmark, Aarhus University:
Søren Kjaergaard, Head of Institute, Principal Investigator on Cooperative Agreement
Eric Parner, Assoc. Prof. at Dept of Biostatistics
Carsten Obel, Assoc. Prof. at Dept of General Medicine
Nils Anderson, Technical Coordinator

Poul Thorsen, USA, Atlanta

Editorial Note: It would be very beneficial for future calls if during the course of conversation individuals identified themselves. This will greatly assist with capturing appropriate call notes and task lists.

Future Conference Calls: Future calls will be scheduled every two weeks. After today's call Marshalyn reviewed her calendar and found that she had multiple conflicts with the every other Tuesday, 8am (eastern) day/time. Santrell Green, the CDC/DDB Secretary has sent out a query, through 'Doodle', to identify best possible ongoing date/time for continued conference calls (calls to be scheduled every other week).

Action List/To Do Items (consolidated listing):

1. Søren and Carsten to provide an SSI update on our next call.

2. Poul is requested to provide Aarhus University a copy of all permissions in his files ASAP.

3. Carsten and Eric will be responsible for securing all appropriate permissions and data management across the project.

4. Marshalyn will contact Peter Uldall regarding the CP registers.

5. Søren, Erik and Carsten will also connect with Peter Uldall regarding the continuation for 2009 and the completion of the data collection (CP register).

6. Aarhus University to provide an update on a future call regarding the DNBC Based Studies.

Coleen/Update: Coleen provided an update to the group. From her perspective it appears most of the below activities have been completed. She sees this as a very productive project. The initiation of this bi-weekly call schedule can also been seen as a second phase of the project. This will allow other CDC folks to collaborate in this project. Additional Denmark individuals may also engage in the project.

Current Funding: Currently funds are allocated for the continuation of the laboratory work (David Hougaard) and to support the analyses of the data currently in hand (support to the CP Registry and Autism activities).

Søren/Update: David H is working on some important activities at SSI. Carsten will be meeting w/David H soon to get some additional information on the project; Carsten will provide an update at our next phone call.

TO DO: Søren to provide an SSI update on our next call.

CP Registry. Søren believes that the data collection will be completed this funding period. In the future recommend we use some of the meeting time to discuss how to use this data in future analyses.

Carsten and Eric have been through quite a few discussions to understand the projects. Søren asks Poul's help to identify the 'original' permissions for these projects.

TO DO: Poul is requested to provide Aarhus U a copy of all permissions in his files.

The discussion now focused on the various projects:

CP Update

Marshalyn had talked about the number of cases yesterday. She realizes it is a small number. Initial thought would be maybe do all spastic cases (271 spastic cases).

Coleen asked if there are data dictionaries available. It was confirmed by Diana that there is a CP case control list and a variable list, which could be retrieved upon request.

A general question was asked if there were any additional analyses possible? Diana mentioned she can share information on any additional risk factors that may be worth exploring. She mentioned one area not explored at all is maternal medications received during pregnancy. Sample was on gestational age – not birth years. The sample started in 1982; the last year was 1990. Note – this information was gathered for only the eastern part of Denmark. There are cases in the western part of Denmark but they are not a part of this study.

CP registry data

Coleen asked if we needed permissions if we just wanted to just review the CP registry data. Søren is certain that the CP Registry has received approval. Per Diana they received individual approval for the cases and controls. Per Poul approval from the committee was received every year up until 2005.

Marshalyn asked about a detailed variable listing from the CP Registry. It was noted that Peter Uldall can provide this listing. Poul also stated he may have a copy. Poul also mentioned that he had also developed a code book.

CP biomarker data

Søren asked where the data are for these projects? He wants to be sure that the data are at Aarhus University and safe and to ensure that all permissions are updated and that there should be established a steering committee including members from CDC as well as Aarhus. Søren asked this question of Poul and Diana to provide a historial perspective. Carsten stated he does not have the data. It was noted that SSI manages the biological data since it falls under their responsibility. SSI has the original files at their facilities.

Coleen asked if Aarhus University has access to the case control study data? Søren is not sure right now.

Coleen believes the data should be kept secure in one place. Søren believes that the data should be kept in Aarhus University unless the permissions do not allow it. Søren wants to have the data permissions and data management organized and be secured on the Citrix server..

Permissions

Carsten mentioned that additional permissions need to be received if the western part of Denmark data would be used in additional analyses. It was noted that the original project was approved by the Denmark committee in 1991. At this point they need to request an additional approval. The permission is required from the Scientific Ethical Commite(this organization is outside of Aarhus University).

Poul mentioned the original PI (Jes Vestergaard), who has the permission to the project on inflammatory biomarkers and CP He is currently in Norway. The permission now needs to be transferred to someone else. Poul believes the permission will be given to David Hougaard/SSI (permission transfer ongoing).

TO DO: Carsten and Eric will be responsible for securing all appropriate permissions and data management across the project.

TO DO: Marshalyn will contact Peter Uldall regarding the CP registers. Søren believes that contact is a good idea. It was also suggested that when Marshalyn contacts Peter Uldall request she also keep Carsten and Eric as cc's on correspondence to keep them in the loop.

TO DO: Søren will also connect with Peter Uldall regarding the continuation for 2009 and the completion of the data collection.

Autism Update

Autism register data
Marshalyn asked if Aarhus University can work with Danish Psychiatric Data. Poul stated that this is the registry based data regarding vaccines. Permission should already be in place from the National Board of Health since this was initiated in 1999. Marshalyn verified that we can get all new permissions for anything related to autism. Eric and Carsten will be working hard to ensure we get all needed permissions.

Danish National Birth Cohort (DNBC) Based Studies

Marshalyn had questions regarding these studies. She verified that there was no medical abstraction of the autism perinatal records. She asked what is available from the DNBC?

Carsten verified that there was no abstraction of the perinatal data (on autism). Only the CP and some of the controls are finalized and only the registry data available. All of the data in the DNBC are available.

Coleen verified that they have finished the CP abstraction and are working on the controls. Anything from the DNBC is available (interview data).

Diana asked for an update of the subcohort (control) for CP the case-control study.

Carsten and Eric report that in total 162 children with CP were selected to have their medical record abstracted, of which 127 have been abstracted. A total of 1330 controls were selected of which 1203 have been abstracted.

TO DO: Aarhus University to provide an update regarding the DNBC Based Studies on a future call – especially on the abstractions performed at Skejby Hospital - QDOCS.

Laboratory biomarker panel development:

Permissions

Diana noted that no permission is required. She would appreciate an update from David Hougaard. Carsten mentioned that they would need a permission for access to a certain patient group.

Carsten has not found the original approval for completing this study. He is looking for Poul for original approvals for the Autism studies. Poul mentioned that there were multiple studies put together in one package. Poul cannot find the original permissions. It was noted that the data protection agency approval is in place.

Carsten cannot find any permission on the biomarker study. It was noted that Kristine Svedgaard has send them a letter suggesting that this study received its permission in 2003. Poul stated that if folks are in doubt about the permissions then Aarhus University should secure new permissions.

Poul believes that there has been confusion on the permissions. Carsten believes we do not have permissions for the autism disorder case control study.

Poul suggested that Aarhus University may want to check with Kristine regarding the permissions; she may have tried to secure permission.

Other possibilities:

Marshalyn mentioned these calls will be ongoing. The tasks right now are to gain an understanding of the current status of the activities. At this point we cannot talk about what additional analyses to be completed without a more thorough understanding of the various projects.

Diana would like to talk with David regarding the panel development and regarding what analytes he's prepared. She would also like to know what samples would be available for future studies.

Søren would like an update regarding what David's next step will be regarding the use of these biomarkers.

Wojcik, Joanne (CDC/CCHP/NCBDDD)

From: Wojcik, Joanne (CDC/CCHP/NCBDDD)

Sent: Sunday, November 29, 2009 11:27 AM

To: (DK) Kjaergaard, Soren; (DK) Obel, Carsten ; (DK) Parner, Eric; Boyle, Coleen (CDC/CCHP/NCBDDD); Rice, Catherine (CDC/CCHP/NCBDDD); Schendel, Diana (CDC/CCHP/NCBDDD); Thorsen, Poul; Van Naarden-Braun, Kim (CDC/CCHP/NCBDDD); Vogt, Robert (CDC/CCEHIP/NCEH); Wojcik, Joanne (CDC/CCHP/NCBDDD); Yeargin-Allsopp, Marshalyn (CDC/CCHP/NCBDDD)

Cc: Wojcik, Joanne (CDC/CCHP/NCBDDD); Green, Santrell (CDC/CCHP/NCBDDD) (CTR)

Subject: RE:REVISED Denmark Call Notes - November 10, 2009 - Next Call Scheduled for November 30th (8am Eastern)

Attachments: [Untitled].pdf; [Untitled].pdf

Good Day: Attached are revised Nov 10th call notes (thank you to Carsten and Erik for updating). Also provided from Carsten and Erik is an update for tomorrow's (Monday's) call.

Agenda for Tomorrow's Call (8am Eastern / 2pm Denmark)

When: Monday, November 30, 2009 8:00 AM-9:00 AM (GMT-05:00) Eastern Time (US & Canada).
Where: Via teleconference (Eastern Standard Time)

Toll Free/Freephone Number :
AUSTRALIA (b)(6)
DENMARK (b)(6)
SPAIN (b)(6)
SWEDEN (b)(6)
USA (b)(6)

Leader Passcode : (b)(6)
Participant Passcode :

Review of Action Items from the last call (some updates provided in Carsten/Erik's document - attachment 2).

Action List/To Do Items (consolidated listing from Nov 10th call):

1. Søren and Carsten to provide an SSI update on our next call.
2. Poul is requested to provide Aarhus University a copy of all permissions in his files ASAP.
3. Carsten and Eric will be responsible for securing all appropriate permissions and data management across the project.
4. Marshalyn will contact Peter Uldall regarding the CP registers.
5. Søren, Erik and Carsten will also connect with Peter Uldall regarding the continuation for 2009 and the completion of the data collection (CP register).
6. Aarhus University to provide an update on a future call regarding the DNBC Based Studies.

Other Topics

Proposed future calls - 8am-9am EST on the following bi-weekly dates through March.

November 30

December 14 (one call in December due to the Christmas holiday)

January 11, 25

February 8, 22

March 8, 22

Wojcik, Joanne (CDC/CCHP/NCBDDD)

From: Boyle, Coleen (CDC/CCHP/NCBDDD)
Sent: Tuesday, June 16, 2009 10:41 AM
To: 'Ulrik Kesmodel'; Denny, Clark (CDC/CCHP/NCBDDD); Wojcik, Joanne (CDC/CCHP/NCBDDD); Jakob Grove; Tina Røndrup Kilburn; Hanne-Lise Falgreen Eriksen; Åshild Skogerbø; Søren K. Kjærgaard
Subject: RE: Agenda and minutes from meeting 9 June 2009

Ulrik: Thank you for summarizing our meeting so well. I will work with Clark to re-engage the bi-weekly conference calls. When I met with Erik Mortensen on Friday he emphasized the importance of finalizing the data analysis plan quickly so that the analyses could proceed in a uniform manner. Additionally, I have checked on the status of our contract with Bradley Sharpness. We are finalizing the details of the contract and he should be available to work with the project soon.

Regards,

Coleen

Coleen Boyle, Ph.D.
Director
Division of Birth Defects and Developmental Disabilities National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention 1600 Clifton Rd., MS-E-86 Atlanta, GA 30333

cboyle@cdc.gov
404-498-3907
fx: 404-498-3550
cell: (b)(6)

(Delivery Address: Bldg 1825, Rm 3029, Century Center Blvd. Atlanta, GA 30345)

-----Original Message-----
From: Ulrik Kesmodel [mailto:UKES@SOCI.AU.DK]
Sent: Tuesday, June 16, 2009 4:13 AM
To: Boyle, Coleen (CDC/CCHP/NCBDDD); Denny, Clark (CDC/CCHP/NCBDDD); Wojcik, Joanne (CDC/CCHP/NCBDDD); Jakob Grove; Tina Røndrup Kilburn; Hanne-Lise Falgreen Eriksen; Åshild Skogerbø; Søren K. Kjærgaard
Subject: Agenda and minutes from meeting 9 June 2009

Dear all,

Thank you for your contributions to our meeting last week. Please find attached the agenda and minutes from the meeting. If you have any comments, please let me know.

Best regards
Ulrik

Ulrik Schiøler Kesmodel
MD, PhD, adj. associate professor, chairman of the Danish Epidemiological Society School of Public Health, Department of Epidemiology University of Aarhus Bartholins Allé 2
DK-8000 Århus C

Department of Obstetrics and Gynaecology Aarhus University Hospital, Skejby
Brendstrupgaardsvej 100 DK-8200 Århus N
Tel: +45 8949 5566 or mobil (b)(6)

Exhibit 19

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date June 8-12, 2009

From CDC, NCBDDD, Division of Birth Defects and Developmental Disabilities Staff

Subject Site Visit, June 8-12, 2009, Danish Agency for Science, Technology, and Innovation, and Aarhus University, 5 U10 DD000230-03

To File

BACKGROUND: This grantee is completing Year 03 of a 05 Year Project Period.

PURPOSE: The purpose of this site visit was to meet with the grantee Principal Investigator, senior scientists, and the rest of the team to receive an update on the status of the project activities and project personnel structure in wake of recent personnel changes and to also review the current status of the scientific progress on the cooperative agreement activities.

ATTENDEES:

Coleen Boyle, PhD, Director, DBDDD, CDC
Clark Denny, PhD, Epidemiologist, PRB., CDC
Joanne Wojcik, BA, Deputy, DDB, CDC

Aarhus, Denmark Site Visit Location:

Jacob Grove, PhD, Biostatistician, Aarhus University
Dorte Hvidtjørn, PhD, Candidate, Aarhus University
Clause Svaerke, PhD, Statistician, Aarhus University
Hanne-Lise Eriksen, PhD, Candidate, Psychologist, Aarhus University
John Villadsen, Research Assistant, Skejby Hospital
Søren Mogensen, MD, Dean, Health Sciences, Aarhus University
Søren Kjaergaard, PhD, Head, School of Public Health, Aarhus University
Dorthe Hejl, Accountant, Aarhus University
Annette Bachman, Head of the Secretariat, Aarhus University
Ulrik Kesmodel, MD, Ob/Gyn, Aarhus University
Åshild Skogerbø, PhD Student, Copenhagen University
Tina R. Kilburn, MSc, PhD, Aarhus University
Lars Jorgen Østergaard, MD, PhD, DMSc, Aarhus University Skejby Hospital
Inge V. Arbs, Project Coordinator, Aarhus University, Skejby Hospital
Jørgen Jørgensen, Director, Aarhus University

Lars Ove Jensen, Police Assistant
Peter Andersen, Vice Police Commissioner
Anne Christiansen, Administration, DASTI
Moller Madsen, Chief Lawyer, Aarhus University

Copenhagen, Denmark Site Visit Location:

David M. Hougaard, MD, DSc (Med) Consultant, Statens Serum Institute
Anne Christiansen, Head of Secretariat, Danish Agency for Science, Technology and Innovation (DASTI)
Inge Maerkedahl, Director, DASTI
Soren Munk Skydsgaard, Head of Administration, DASTI
Charlotte Elverdam, General Counsel, DASTI
Katja Gunnertoft Bojsen, Head of Section, DASTI
Erik Lykke Mortensen, PhD, Associate Professor, Copenhagen University

In Briefing: Coleen Boyle and Joanne Wojcik met with key Aarhus University staff, Søren Mogensen, Dean, Health Sciences, and Søren Kjaergaard, the Head of the School of Public Health.

Søren Kjaergaard, the designated new Principal Investigator once the award is relinquished from DASTI and transferred to Aarhus University will be involved in future meetings with project staff. Concurrently, Coleen Boyle has also taken over as the CDC lead for this project. In collaboration with CDC and Aarhus University the project will be reviewed and adjustments will be made to ensure key project activities continue to move forward. Also noted was Diana Schendel may continue with Autism/Cerebral Palsy activities and Sonja Rasmussen will continue to be the lead for Down Syndrome activities.

The ongoing external audit of grant funds was discussed and an update provided. There is also an ongoing investigation verifying bills and checks processed as a part of this award. This investigation is taking place to ensure no grants funds were inadverently directed to inappropriate accounts.

A review is also taking place concerning two invoices that were submitted by Emory requesting grant funding to support activities in Atlanta. These invoices requesting reimbursement for salary and other expenses paid by Emory University were denied by Aarhus University. Initially Aarhus University requested additional detail regarding these invoices. Upon their review of the detailed invoices they noted salaries were requested for various staff members. It was noted that Poul Thorsen was provided a full salary by Aarhus University up until March 2009. Aarhus University provided CDC documentation verifying his payroll status.

Reviews of the funding breakout as well as the deobligation of Spina Bifida dollars were also discussed. The upcoming change of institution will transfer $1,100,000 from DASTI to Aarhus University.

Søren Kjaergaard will work with his staff to ensure appropriate breakout and take into the account the restrictions placed on the initial year 03 award. He will also be looking into identifying a person with a scientific background to assist him with oversight of the activities. This would then allow him to be listed on the award for a minimum amount of time, estimating approximately 5 to 10% effort (salary).

Grant Application Change of Institution / Budget Discussions: Coleen Boyle and Joanne Wojcik met with Søren Kjaergaard, Dorthe Hejl, and Annette Bachman.

CDC/PGO can expect the revised change of institution application by the end of June 2009. This application will show an effective date of February 1, 2009. Dorthe mentioned that Aarhus University already has an institution DUNS number; this will help facilitate the transition. Aarhus University will ensure that budgets will be broken out into subcontracts. The University will also include indirect costs – U takes 4% (they will show this amount as as other costs). The University will also provide a breakout of costs (by spreadsheet) showing allocations by "project'. The University was reminded to ensure appropriate documents are submitted regarding their Banking (their Bank will be required to physically sign the documents – then they will need to forward the completed banking form back to PGO). Dorthe will discuss with Randolph appropriate bank for transactions. Joanne believes Aarhus will need to ensure the bank has a U.S. Branch.

Søren Kjaergaard mentioned that he will be bringing the NANEA offices back to the University – versus their current arrangement offsite in a leased house. This way the program staff will be closer to the institute to allow them to be more integrated into the Institute activities. Søren has received a potential promise for space in the white building next to the offices.

Lifestyle Project Update: Coleen Boyle, Clark Denny, and Joanne Wojcik met with Lifestyle Project staff for a day long update of activities. Staff presenting included - Jacob Grove, Dorte Hvidtjørn, Clause Svaerke, Hanne-Lise Eriksen, Tina Kilburn, Åshild Skogerbø, and Ulrik Kesmodel.

Summary: Ulrik Kesmodel provided an historical overview of the Lifestyle Project. The psychologists meet monthly. Every 6 months there is a meeting of the entire project staff to discuss larger issues and any changes that need to be made to keep the project moving forward. An experts meeting was held in 2002 and 2003 when the project was first beginning. During data collection the psychologists met every six months to examine inter-rater reliability. Eleven psychologists and 30 physical therapists collected the data but the number of evaluations per psychologists varied. A background/methods paper was accepted with minor revisions by the Scandanavian Journal of Public Health. Ulrik will send Coleen Boyle and Soren K. an updated copy of the draft publication later this week. Physical therapists did motor tests of the first half of the children (until they ran out of money). They also held inter-rater reliability meetings every 6 months

In 2005 an additional diet sample was collected. Jakob Grove, the statistician, does not have the information on how the sample was collected. It can be included in the larger study but may not add much power.

In 2008 the first PhDs were completed by Tina Kilburn and Mette Underbjerg. The last child was tested in June 2008. They have spent this past year cleaning the data – currently the data are almost completely cleaned. The cleaning of the Home Environment Index and the Child Health Index are incomplete because the elements that will comprise them have not been agreed upon.

Alcohol & IQ - Hanne-Lise Erikson provided an update of her project. The original deadlines for her three articles: 7/31, 8/31, and 9/30 2009 – will probably be delayed 2-3 months. On April 30, 2010 she will be handing in her PhD thesis. Last fall the opportunity to collaborate on her projects was offered to CDC but there was no follow up. Coleen will ensure there is CDC identified collaboration.

Alcohol & behavior (ÅS) - Åshild Skogerbø at Copenhagen University is now working on her data analysis. She is looking at high to low alcohol exposure. The alcohol exposure categories are fixed based on the sampling procedure. The (Strengths and Difficulties Questionnaire) SDQ test has been thoroughly analyzed with foreign population norms. The proposed timeline for completion of her papers is from Nov 2008 – Oct 2011 (due to maternity leave). She will be starting the data analysis after this week and is working on final data cleaning. She is preparing 4 papers and then her thesis from March 2010 through July 3, 2010. Her plans are to have out the first 2 articles by November 2009. She has 1784 mother-child dyads. Jorn Olson is looking into following up the children at age 12. There has been no direct collaboration from CDC with this part of Ashild's project. The Prevention Branch is developing with the Danish researchers an overall paper to look at all of the neurodevelopmental functioning.

Data cleaning process - Hanne-Lise Erikson. Hanne-Lise summarized the data cleaning process. Most of the tests were collected on a hard copy. Keyers input the data into the computer. Data was not double keyed because error rate was very small. Occasionally double keyed it is still kept at a very low error rate.

Coleen was provided a hard copy of the lifestyle questionnaires in Danish and the "overview of cleaned variables'. Hard copies of the files are kept in the NANEA basement at Aarhus University. The analytic data set has the cleaned variables. Any other variables would need to be cleaned before analyzed. DNBC data are already expected to be cleaned.

In response to Coleen's questions, NANEA believes that it is possible to get secondary data sets for folks to complete some analyses. All of the major outcome and major covariates are included in the initial 'overview of cleaned variables' document.

Two sections have not yet been scored: the draw a person and photographs of the children. Dysmorphology based on the photos have not yet been touched or scored. They have photos of both mothers and child.

List of covariates - Jacob Grove: They still need to get some variables from the DNBC.

Publication plan - Ulrik Kesmodel: Showed a planned papers slide to the group. The long term plan was previously formalized and agreed upon by all. Mette will finish her papers even though she has a new position elsewhere. Nanna decided not to finish her motor function papers, to apply for funding, or to finish her PhD. In order to get Nanna's papers written Ulrik Kesmodel personally will be writing papers #15 and #16 and #14 will be eliminated. Lene's papers regarding diet. She left the project at the end of May. To be discussed this afternoon. Coleen has someone at CDC who could work through the diet paper – she is very interested. Ashild's #18 and #19 papers have been deleted.

Coleen has requested Ulrik provide an updated papers listing. We discussed the overall paper, #24. Poul Thorsen / Ulrik Kesmodel will be coordinating that paper. The Ph.D. students need to write their papers first; however, we discuss developing the final paper in parrallel. The date for a final draft of the overall paper is July 31, 2010 but this may need to be pushed slightly.

Number 25 is a literature review that has nothing to do with the project. Coleen will verify that CDC has completed the literature review. Coleen believes that Molly Cogswell completed this literature review?

CDC will reestablish regular phone calls with Aarhus University scientists. Calls will include CDC, Denmark, and Bradley Skarpness. Soren K and Coleen will also participate on a few of the initial calls.

Analysis plan – Jacob Grove – The analysis plan does not include motor function because the data is only on 750 children. Coleen may want to look at motor function on just that component. Bradley Sharpness/Battele (on a volunteer basis) is working on the low to moderate alcohol exposure analysis plan. Stage I is the analysis of individual outcomes. Stage II is the mixed-model analysis of variance. There will be multiple dependent variables. Concern that they may not be able to get the Battelle algorithms; Coleen believes it has been solved. Battelle will provide NANEA the software and will help Jacob Grove with the analysis. STATA is used by NANEA. The Battelle software is stand alone software. To look at the data folks would need to come to Denmark. DNBC would ultimately own the data. Perhaps an analytic database may be able to be analyzed in the USA; Coleen suggests we explore further with Denmark.

Steering committee - Ulrik Kesmodel: Committee to help with decisions where there may be conflicts. The current members are Ulrik Kesmodel, Erik Mortensen, and Poul Thorsen. Suggest that CDC also be included. At this point Coleen Boyle was added to the committee to represent CDC.

Future projects, including diet? - Ulrik Kesmodel: Technically the diet belongs to the national birth cohort. Will be planning a meeting around June 24th to discuss how to move the diet part forward. Will discuss various papers that can be written. Professor - Sjurdur Olsen (SF Olsen – for publications). Ulrik will get with CDC after that meeting to provide an update and come up with a strategy. Dietary data that was collected. Sjurdur and his collaborators have cleaned most of it. Ulrik needs to finalize an agreement with Sjurdur.

Notice of Award for Year 03 – The psychologists will not clean the movement ABC. Comment – two physical therapists are cleaning the data – many more than three variables.

August 31 – is the date for the cleaned data set. Jan 1st – complete analysis for large overall paper. Analysis part will be delayed three months. Coleen will send Ulrik a paper as an example of a comparable type published in the New England Journal of Medicine. Binge and moderate drinking may be published together or separately.

Question – has CDC thought of a way to keep the students involved in the future with the data analysis? Is CDC open to any ideas? Coleen is open to any suggestions.

Prevention Research Branch's goal is to get paper 24 out as soon as possible.

Autism/Cerebral Palsy Medical Records Abstration Update: Coleen Boyle and Joanne Wojcik met with Aarhus University Hospital, Skejby. Lars Jorgen Østergaard and Inge V. Arbs provided an update concerning their activities related to this grant. Currently they are abstracting data on cerebral palsy children. All of their abstractors are 4th medical students. Twelve students were trained last year and they plan on training an additional group of new students this year. The Medical students take a 2 day introductory course where they then are given the opportunity to score high enough on test histories. Once they succeed in scoring, they are then given a license to work in "Q Docs". They gain from this experience more indepth knowledge related to histories and medical, records. The Q Docs server is located at Skejby. The have approximately 24 laptops that transmit through a secure data network to the server at Skejby.

Lars mentioned that there is no hospital review board but they do have an ethics committee. He also mentioned that Poul Thorsen received all human subjects approval for this project.

Cerebral palsy abstraction started last summer 2008. The students are paid by the review as well as their travel. For offices far off they are paying for records to be delivered to the Skejby offices. They are completing the entire country of Denmark with this CP study. Their goal is to have 21 students. For healthy mother and child they receive 175,00 kr if a case they receive 250,00 kr per file. Medical students work an average of 6 hours a week. Currently they can get approx 1 ½ - 2 years of work out of the students.

They also have a student to complete upgrades on the server. John Villadsen also helps with the technical activities. He accesses the CPR register to complete activities. John has computer and data management skills. He started here at Skejby full time late summer. He is in Skejby Mon and Tues and the rest of the week at PM17. John also worked with the lifestyle project on the abstraction, reviewing the data and helping with the cleaning.

Regarding the quality control process there is no re-review of records. They are hoping that Poul Thorsen can come back to Denmark this summer to complete the re-review. There are no range edits or logic edits have been setup for the files. They realize that there will be quality control at some point. Last year they took 15 records – and compared for quality control. They anticipate completing this same exercise again this year. Coleen suggested that Claus Svaerke may be able to assist with some of the logic edits.

TO BE COMPLETED
25 maybe add'l
35 cases that they know w/CP in the western part of the country.
60 still need to abstract

COMPLETED
East 44
West 70
Cases 114

1122 finished
453 yet to be completed

1575 total CP

We are unsure if they can use the cerebral palsy controls for the autism abstraction. They have not yet started the autism abstraction. Lars mentioned that all of their data will be provided to Soren K, at his request.

Their abstractors also helped with the twins study. Apparently, Dorthe needed information for her study. Info has not been electronically entered but is currently kept in boxes. Dorthe still needs to pick up the data.

Lars – thinks an epidemiologist may be more beneficial for 'on-site leadership'. Lars mentioned there is also a very strong epi department at the hospital (dept headed by Henrik Scorensen) – department of clinical epidemiology.

According to the timeline they are to complete the cerebral palsy cases and the autism cases are still to be done. Lars will send Coleen an electronic copy of the protocol. According to the timeline it appears the controls are for both CP and autism cases. It is unsure at this point where the list for the Autism cases is located.

Coleen Boyle 1 on 1's with Claus Svaerke and Jacob Grove took place.

Grants Documentation Discussion: Coleen Boyle and Joanne Wojcik met with key Aarhus University, DASTI, and local enforcement officers to discuss grants documentation. Staff included: Dean Søren Mogensen, Søren Kjaergaard, Jørgen Jørgensen, Lars Ove Jensen, Peter Andersen, Anne Christiansen, and Moller Madsen.

Søren Kjaergaard provided an update regarding the Emory documentation. Søren Mogensen provided an overview of the three pieces of correspondence from CDC/PGO in question. Anne Christiansen received the first document in June /July 2008. She did a thorough accounting last year. She noted the third letter original was on USA sized paper. The police noted that they will need to examine original documents; they can't make statement viewing copies. A potential case may include – forgery – fraud – and/or embezzlement (if funds were redirected/it would be misuse of trusted position at this point).

At this point the crimes regarding the three documents appear to have been committed in Denmark. The police are just starting their investigation and need to investigate DASTI, AU, Odense Hospital. CDC documents may be needed. If that is the case the police will go through DASTI. Denmark police may also send someone to the United States to talk with Poul Thorsen.

DASTI is working on getting a full report from Odense Hospital. DASTI is expecting the information from Odense by Monday, June 15th.

Lifestyle Project Update - Coleen Boyle and Clark Denny met one on one with students working on the Lifestyle Project.

Change of Institution Discussion - Joanne Wojcik met with Dorthe Hejl to review the change of institution documentation. Joanne showed Dorthe where to download needed forms. They also discussed the need to establish separate contracts and show contract details in the change of institution package.

Wrapup Meeting at Aarhus University: Coleen Boyle and Joanne Wojcik met with Dean Søren Mogensen and Søren Kjaergaard.

Coleen and Søren M will continue to discuss needs of the projects and how to best move the projects forward towards completion.

Laboratory Analysis: Coleen Boyle and Joanne Wojcik visited the Statens Serum Institute to meet with David M. Hougaard.

David had provided a biomarker development update to Coleen prior to this meeting. Christine (biologist) just finished her PhD 6 months ago. They also hired a new biologist – Nanna Larson – to develop the biomarker panel for autism.

One half of panel is done on dried blood spots. They currently have 20 markers for the autism panel.

David anticipates having the autism panel in place in one year from now.

Last year they received all of their money in January 2009. Their budget last year was for 1.2M DK (approx $250,000) David also has consultant support for himself for approximately $20,000 of his salary. SSI provided invoices every few months; they sent their bills directly to Soren K.

Nanna Larson had to be moved because of a lack of dollars. This is Nanna's doctoral dissertation work.

They currently have 900 autism samples from the biobank. Diana Schendel has this information and is writing a paper.

FY 2009 from PT
Cost for next year

DH	20,000
Lab	60,000
Post Doc	80,000
Something	50,000
Total	210,000

Needs for FY 2010

It would cost an add'l $20,000 to run the samples. This activity would take approximately one month to complete (Feb 2010 timeframe).

Coleen will identify scientific support to assist. David mentioned that he works with Bob Vogt at NCEH.

David also mentioned they had run 600 cerebral palsy cases; that paper has not yet been written. He believes Poul Thorsen should be the first author; Poul currently has the data. We do not believe David H has the data. Coleen mentioned that she was aware of this paper since it is on Diana Schendel's to do list of publications. Coleen will assist to expedite its completion.

DASTI/Business Management/Administration: Coleen Boyle and Joanne Wojcik visited the DASTI Offices to meet with Anne Christiansen, Inge Maerkedahl, Soren Munk Skydsgaard, Charlotte Elverdam, and Katja Gunnertoft Bojsen.

DASTI requested an outside audit on Odense records. They expect to receive the results of this audit by June 15th. DASTI will then have a follow-up meeting by June 23rd. At this point it appears Odense is having a deficit also – now approx $2-3M loss overall.

Pending Administrative Actions

Old
FSRs not accurate – working on them
Getting Odense figures
Working on closeout documentation

New
Since June 2007
Working on accounting
Annual reports

Anne Christensen will be on maternity leave at the end of July.

Odense external auditor – Deloitt
Aurhus U external auditor – Price Waterhouse

Coleen will check with Aarhus University regarding who owns the data. She is unsure if there would be any access challenges. Anne believes Aarhus University is also looking into this. Anne will check back at the end of June regarding the outstanding reports.

Lifestyle Supervisor Meeting, Copenhagen University: Coleen Boyle and Joanne Wojcik met Erik Lykke Mortensen. Coleen re-iterated that Paper 24 is the main paper. Ashild is planning to be on leave for approximately 1 year. Erik mentioned he is meeting w/ Ashild on Monday to discuss a suitable game plan. He will request Ashild not change the order of her papers since we will need the main information for the larger paper. Mette and Tina have draft papers of their papers based on their dissertation work. Erik M believes the big paper should be included as soon as possible. Erik M was in agreement to restart the bi-weekly phone conferences with CDC Last year's Atlanta meeting was very good. It may be time to come to Atlanta to discuss again.

Data analysis plan needs to be finalized now. Coleen suggested email may be a good way to finalize the plan and identify any outstanding issues. We discussed a possible Sept 2009 meeting in Denmark together to discuss the preliminary analyses. Clark Denny and Jackie may participate in the Denmark meeting.

Coleen suggested there be a structure to the bi-weekly calls to include:

Data plan discussion
Discussion on the analyses

1 or 2 per call	IQ
	Exec Function
	Behavior
	Processing

All analyses should use the same analysis plan, same covariants

A webinar during calls may be also help facilitate involvement and communication between CDC and Denmark. We will need someone from CDC to ensure calls and tasks are tracked / noted.

FY 2009 budget includes Erik's salary (small portion) plus travel for himself.
Ashild's salary is covered by a University of Copenhagen grant. Aarhus University pays Ashild's travel expenses directly to her. Ashild is an Aarhus University employee.

Actions Items:

CDC

Joanne to verify human subjects IRB(s) provided by grantee.

Joanne/Coleen to verify CDC IRB for project is one approval or each project approved separately?

Coleen to ensure there is CDC identified collaboration for the Alcohol & IQ (Hanne-Lise's) Project.

Coleen to get name of test requested by Jackie Bertrand.

Coleen to verify if Molly/CDC has completed the literature reviews (#25).

Joanne to check into the requirement for a public use data set requirement for international grants.

Coleen to identify any potential CDC epi/scientific support for Laboratory activities

CDC/Lifestyle Project – Initiate ongoing calls with Denmark scientists.

CDC/Lifestyle Project – Initiate emails to finalize data analysis/publication plan

Aarhus University

By the end of June 2009 provide change of institution paperwork to CDC/PGO.

Ulrik to provide CDC an updated papers listing.

Ulrik to get paper #24 out as soon as possible.

Identify an epidemiologist to assist with the 'onsite leadership' including quality control needed for the CP/Autism abstraction activities.

Identify the number of autism cases there are – and what is the status of this portion of the abstraction. Are they using the same controls? Appear to be based on the timeline.

Identify author to initiate writing of the CP cases laboratory analysis. Poul Thorsen has had the data for 3 years? CDC will explore the possibility for Diana Schendel to assist with the completion of this manuscript.

Identify timing for Fall 2009 collaboration meeting.

DASTI

Old Pending Admin Actions

FSRs not accurate – working on them
Getting Odense figures
Working on closeout documentation

New Pending Admin Actions

Since June 2007
Working on accounting
Annual reports

Provide CDC update re audit results; including providing an English copy of audits from Aarhus University and Odense Hospital to CDC/PGO.

Recommendations:

Change of Institution:

Complete Change of Institution paperwork

Provide needed reports, FSRs, and audit reports

Lifestyle Project:

Finalize analysis/publications plan

Re-Initiate ongoing phone call discussions re analysis and papers

Finalize dates for Fall 2009 collaboration meeting

Down Syndrome Project:

Identify add'l epi assistance

Cerebral Palsy/Autism Abstraction Project:

Complete cerebral palsy activities and ensure appropriate quality control of data. Identify the autism cases and determine how they relate back to the work being done by the laboratory. Assess the costs and usefulness of moving forward with the autism case medical record abstraction.

Laboratory Analysis Project:

Identify epi support for analysis, particularly autism

Identify lab collaboration from CDC

Identify lead author for cerebral palsy biomarker paper; CDC will explore whether Diana Schendel can help finalize this paper.

Exhibit 20

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 develop 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? s 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, dypraxic 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 the 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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Key Findings: Potential impact of DSM-5 criteria on autism spectrum disorder (ASD) prevalence estimates

JAMA Psychiatry has published a new study: "Potential impact of DSM-5 criteria on autism spectrum disorder (ASD) prevalence estimates." Researchers found that estimates of the number of children with ASD might be lower using the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria than using the previous Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria.

You can read the article's abstract here (http://archpsyc.jamanetwork.com/article.aspx?articleid=1814891) . Read more below for a summary of the findings from this study.

Main findings:

- Over 80% of children who met the Autism and Developmental Disabilities Monitoring (ADDM) Network (https://www.cdc.gov/addm) classification for ASD, which is based on DSM-IV-TR criteria, also had documented symptoms that met the DSM-5 criteria (which were published in May 2013).
  - The remaining 20% met the ADDM Network classification for ASD, but did not meet the DSM-5 criteria. However, many of those children were very close to meeting DSM-5 criteria and were missing only one of the necessary symptoms.
  - Children who met the ADDM Network classification for ASD were more likely to meet DSM-5 criteria if:
    - They had a history of developmental regression
    - They had intellectual disability or
    - They had been diagnosed with ASD by a community provider or were receiving special education services under an autism exceptionality, or both
  - There were no differences between boys and girls or between White and Black children in their likelihood of meeting both the DSM-5 criteria and the ADDM Network classification for ASD.
- The findings suggested that estimates of the number of children with ASD might be lower using the current DSM-5 criteria than using the previous DSM-IV-TR criteria.
- As doctors and other clinicians start using the DSM-5 criteria, they might diagnose ASD using new or revised tools or they might document symptoms differently. These changes in everyday community practice could offset the DSM-5's effect on estimates of the number of children with ASD.

Because of the way that CDC's ADDM Network (https://www.cdc.gov/addm) collects data, in the future CDC will be able to use both the previous DSM-IV-TR and the current DSM-5 criteria to estimate the number of children with ASD. CDC also will continue to evaluate the effect of using the DSM-5 on trends in how doctors and other health professionals diagnose ASD and how service providers evaluate and document symptoms as they transition to using the DSM-5 criteria.

About This Study

This study looked at information collected by CDC's ADDM Network. This is the first population-based study (meaning the study used information on thousands of children in multiple communities) in the United States to look at what effect the updated ASD criteria in the DSM-5 might have on estimates of the number of children with ASD.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is what doctors and other clinicians use to diagnose mental disorders among children and adults. It also can be used as a guide in public health for collecting consistent and reliable data. There have been several editions of the DSM since the 1950s; the most recent edition, DSM-5, was released in May 2013.

For more general information about the DSM, please visit: www.psychiatry.org/practice/dsm (http://www.psychiatry.org/practice/dsm) . For more information about the DSM-5, please visit: www.psychiatry.org/dsm5 (http://www.psychiatry.org/dsm5) .

Autism Spectrum Disorder: CDC Activities

CDC is committed to continuing to provide essential data on ASD, search for risk factors and causes of ASD, and develop resources for parents and professionals that help identify children with ASD and other developmental disabilities as early as possible. Please visit CDC's website to learn more about ASD (https://www.cdc.gov/autism) and to find resources (https://www.cdc.gov/ActEarly) for parents and professionals.

Reference for Key Findings Feature:

Maenner MJ, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, Van Naarden Braun K, Kirby RS, Bakian AV, Durkin MS. Potential impact of DSM-5 criteria on autism spectrum disorder (ASD) prevalence estimates. JAMA Psychiatry. 2013.

E-mail Your Friends	Share on Facebook	Share on Twitter
"Children with autism spectrum disorder are not being diagnosed as early as	"Many children with autism spectrum disorder (ASD) are not being identified as early as they could be. Early identification is	"Too many children w/ autism are not being identified as early as they could be. Earlier is better. #ActEarly"

they could be. Learn the signs of autism and get help if you're concerned."

Send an E-mail (mailto:?subject=Facts%20about%20ASD&body=Too%20many%20children%20w%2F%20autism%20spectrum%20disorder%20are%20not%20being%20diagnosed%20as%20early%2

the most powerful tool we have right now to make a difference in the lives of children with ASD."

Share on Facebook (https://www.facebook.com/sharer/sharer.php?u=http%3A%2F%2Fcdc.gov/ncbddd/actearly)

Share on Twitter (https://twitter.com/home?status=Too%20many%20children%20w%2F%20autism%20are%20not%20being%20id

ASD Homepage (/ncbddd/autism/index.html)

- Facts (/ncbddd/autism/facts.html)
  +
- Screening & Diagnosis (/ncbddd/autism/screening.html)
  +
- Treatment (/ncbddd/autism/treatment.html)
- Related Topics (/ncbddd/autism/topics.html)
  +
- Data & Statistics (/ncbddd/autism/data.html)
- Research & Tracking (/ncbddd/autism/research.html)
  +
- Articles & Key Findings (/ncbddd/autism/articles.html)
- Free Materials (/ncbddd/autism/freematerials.html)
- Videos (/ncbddd/autism/videos/index.html)
- My Story (/ncbddd/autism/stories.html)
- Information For Specific Groups (/ncbddd/autism/informationfor.html)
  +
- Links to Other Websites (/ncbddd/autism/links.html)
- About Us (/ncbddd/autism/about.html)

Page last reviewed: April 28, 2017
Page last updated: January 22, 2014
Content source: Division of Birth Defects, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (/ncbddd)

APA DSM5 Work Group Member Disclosure Report

Exhibit 22

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.

Commercial or Other Organization	Year(s)	Relationship	Key(s)
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.

Non-Profit or Advocacy Organization	Year(s)	Relationship	Role

None

Exhibit 23

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

Lookup this article

Keywords:	labor , public health , researchers , research , lifestyle , media , tax evasion , spin , university , economics
Organizations:	Aarhus University , TAX
Locations:	Copenhagen , U.S.

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

Larger image

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.

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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.

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, NANEA plated. 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 moneymen *over there,* and the knowledge, Poul Thorsen access. Based on databases that are full of records of the pregnant woman's lifestyle, work NANEA 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 NANEA 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 NANEA 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.

PS

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This article is recommended by:

Troels Hansen

Comments

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Good tone in the debate

Ole Gerstrøm says:

Berlingske wrote that the unit's research results are not challenged. This conclusion seems premature. From criminology, we know that the typical fraudster will be hooked. It should go on and on.

Research Nanea had such "Proven" lack of correlation between mercury vaccines and autism.

18th March 2010 at. 20:54

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
12. marts 2010 | Om denne artikel

Opslag til denne artikel

Emneord:	arbejdsmarked, folkesundhed, forskere , forskning , livsstil, medier, skattesnyd, spin, universiteter, økonomi
Organisationer:	Aarhus Universitet, SKAT
Steder:	København, USA

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

Større billede

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.

Artikelværktøj

KOMMENTARER (1)
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FACEBOOK

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.

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-lektoren 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 Instituttet. Han er også blandt frontløberne i debatten om, hvordan Danmarks intellektuelle højborge 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 hærge. 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, boltrer 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 agitatorting. 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

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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.

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Denne artikel er anbefalet af:

Troels Hansen

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 kviksølvvacciner og autisme.