Journal of American Physicians and Surgeons
Mission Statement
The Journal of American Physicians and Surgeons, the official peer-reviewed journal of the Association of American Physicians and Surgeons (AAPS), is committed to publishing scholarly articles related to the practice of medicine and to promoting open debate and scientific integrity.

Subscriptions and Advertising
aaps@aapsonline.org

Subscription Rates:
AAPS Members (included in annual dues)
Non-members $75 per year
Institutions $125 per year
Students/Residents $15 per year
Foreign $200 per year (US currency only)

AAPS
Omnia pro aegroto

Copy Editor
Stuart Faxon

Cover Design
Noah Snavely

Typesetting and Printing
A Plus Printing
Tucson, AZ

Website
www.jpands.org

Webmaster
Jeremy Snavely

POSTMASTER:
Send address changes to

1601 N. Tucson Blvd, Suite 9
Tucson, AZ 85716

Journal of American Physicians and Surgeons (ISSN 1543-4826)
is published quarterly.

Correspondence

Why Disqualify the One Who Knows?

When Galileo in Italy claimed that the world goes around the Sun, he was forbidden by the Pope to continue such "heretical" teaching and was forced to recant his belief. No doubt this was because the majority of the Cardinals at that time found the idea too disturbing to their preconceived ideas. Writing to Copernicus, Galileo said, "They will not even look in my telescope."

We would like to think that such philosophically rigid beliefs could not possibly occur in our modern scientific world, yet they do. The so-called "shaken baby syndrome" is one such example of how rigid beliefs often trump scientific facts.

Dr. Archie Kalokerinos travelled all the way from Australia to Orlando, Florida, in August 2004, expecting to give evidence on behalf of Alan Yurko at a hearing concerning the death of his infant son. Alan Yurko had served six years of a life-plus-ten-years sentence in prison based on the diagnosis of shaken baby syndrome, even though there was no evidence that Mr. Yurko or anyone else had shaken the infant. Dr. Kalokerinos believed that the cause of the infant's death was most probably an adverse vaccination reaction.

Despite his expertise and willingness to testify, Dr. Kalokerinos was disqualified as an expert witness on day 1 of the judicial hearing (August 23, 2004) on the grounds that his clinical observations and his clinical opinion were not yet accepted by the majority of physicians!

There have been many reports of severe reactions and deaths following vaccinations of people in primitive societies, as exemplified by Patrick Tierney's book, *Darkness in El Dorado*, concerning the people who live along the Orinoco River in Venezuela. But only one physician has had the opportunity to study a large series of such children, both before and then after specific treatment to prevent such deaths in the same population. Dr. Kalokerinos,[1] working with the Aborigine people of Collarenebri in Australia, witnessed a series of infant deaths following the usual childhood vaccinations. Immediately after the institution of vitamin C supplementation at the time of inoculation, the post-vaccination deaths ceased. This was a seminal event in clinical medicine.

The Aborigines had no experience of and no natural immunity to diseases of the Western world. Moreover, the children were malnourished, had perpetually runny noses, and were living in primitive sheds, known as humpies, or in derelict automobiles. Their death rate following vaccinations had been appalling. How could anyone claim that Dr. Kalokerinos, with his 50 years of pertinent experience, was not fit to be accredited as an expert witness, just because other physicians had not lived through his experience and have not yet accepted his teaching?

I do not believe that the legal profession was responsible for restricting Dr. Kalokerinos's freedom of speech. The court was undoubtedly following the opinion of physicians. One would have thought that the court should have allowed a dissenting opinion. Why disqualify the only one with knowledge based on his first-hand experience? We cannot recreate a controlled human experiment; it would be quite unethical to place some of the infants at such a disadvantage.

It is most unfortunate that one of the very few physicians with the experience to provide evidence for the defense was denied the right to speak in court; Dr. Kalokerinos must have felt the insult of Galileo as he flew back to Australia.

Fortunately for Mr. Yurko, other experts were allowed to testify and stated that the infant's death could have been resulted from many causes other than

shaken baby syndrome, and that the autopsy had been totally inept. As a result, the court was convinced that Alan Yurko deserved a new trial.

C. Alan B. Clemetson, M.D.
New Orleans, LA

[1] Kalokerinos A. *Medical Pioneer of the 20th Century*. Braeside, Melbourne, Victoria: Australia Biological Therapies Publishing Pty Ltd; 2000.

Drugging Cardiovascular Disease

J. Philip Smith, M.D., and Karen Cosper, R.N., would have us believe that diet and exercise, plus aggressive use of statin drugs to lower LDL cholesterol levels, anticlotting agents, and antihypertensive drugs, collectively would reduce the risk of cardiovascular disease (CVD) by up to 80%.[1] They have literature citations that appear to back their claim.

If "exercise and dietary changes are both effective and inexpensive," as they state, it makes no sense that three kinds of drugs are needed as well. The usual low-fat diets recommended by authorities for the last 45 years have been shown to be ineffective.[2] On reexamination, the Harvard Alumni Health Study results on exercise (their ref. 15) were found to be biased[3]. In general, people who are not too sick or depressed are active on their own volition. This self-selection process negates the reported results of most epidemiological studies touting exercise.

Smith and Cosper cite the HPS trial (their ref. 6) to show that reductions in LDL cholesterol levels by simvastatin are associated with a 25-35% reduction in RR of stroke and heart attack. In fact, this trial shows an absolute risk (AR) reduction of just 0.36% per year in all-cause mortality in very sick patients. The J-LIT trial using simvastatin showed that the subjects with the lowest achieved levels of total cholesterol or LDL had the highest all-cause mortality.[4] A recent study from the LDS Hospital and University of Utah, Salt Lake City, confirmed that statin use improved the survival rate among 651 patients, 75% male, who had 70% blockage in at least one coronary artery only when infection by cytomegalovirus was present, or when inflammation was severe. There was no survival benefit when both were absent. This finding strongly supports the hypothesis that cholesterol lowering was irrelevant.[5] Using the 0.15%/yr drop in AR for atorvastatin in the ASCOT trial, the chance of not dying in 1 year would be improved by 1 in 667.[6] Only 25.4% of persons prescribed a statin for primary prevention of CVD continued it for more than 2 years. Only 36% of patients receiving a statin for secondary prevention of CVD, among those with chronic CVD without a non-fatal myocardial infarction (NFMI), continued for more than 2 years, as did only 40% of those with an NFMI.[7]

In parallel with the statin drugs, half of the users of antihypertensive drugs discontinue them within a year.[8] In the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), 12.4% of patients on isradipine (a calcium channel blocker) or hydrochlorothiazide (a diuretic) either with or without enalapril (an ACE inhibitor) quit within 1 year, and 18-20% quit within 3 years.[9] Also, 13-20% quit diuretic or beta-blocker treatment in the MRC trial.[10] The dropout rate was 34-39% in the STOP-2 trial.[11] How extreme can the dropout rate be? In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, in which the baseline average BP was only 156/98, it was 55% for enalapril and 60% for nisoldipine.[11]

The 25% drop in RR of mortality cited by Smith and Cosper for beta-blockers amounts to an AR reduction of only 0.1% in all-cause mortality over several years in trials in a meta-analysis.[12]

The group taking aspirin as a platelet disaggregation agent in a 7-year trial on UK physicians had a RR for total mortality of 1.06 compared with the placebo group.[13] The only trial with separate results for women, lasting just 3.1 years, showed that 3.8% of female aspirin users died compared with 3.4% of non-users.[13] Randomized clinical trials testing aspirin in 5,011 elderly people of average age 72 years, 58% of whom were women, followed for a mean of 4.2 years, showed that use of aspirin was associated with a 4-fold increase in hemorrhagic stroke ($P = 0.003$) and a 1.6 to 1.8-fold increase in ischemic stroke in women, but not in men.[14]

Would that the "magic bullets" of Smith and Cosper actually existed, rather than trials with misleading representation of data![15]

Joel M. Kauffman, Ph.D.
Wayne, PA

[1] Smith JP, Cosper K). The end of cardiology and the curing of Medicare? *J Am Phys Surg* 2004;9(3):92-93.
[2] Kauffman JM. Low-carbohydrate diets. *J Scientific Exploration* 2004;18(1):83-134.
[3] Solomon HA *The Exercise Myth*. Orlando, Fla: Harcourt Brace Jovanovich; 1984.
[4] Matsuzaki M, Kita T, Mabuchi H, et al. Large-scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. *Circ J* 2002;66:1087-1095.
[5] Horne BD, Muhlstein JB, Carlquist JF, et al. Statin therapy interacts with cytomegalovirus seropositivity and high C-reactive protein in reducing mortality among patients with angiographically significant coronary disease. *Circulation* 2003;107:1-6.
[6] Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-1158.
[7] Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002;288:462-467.
[8] Cohen JS *Overdose: the Case Against the Drug Companies*. New York, N.Y: Tarcher/Putnam; 2001.
[9] Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). *JAMA* 1996;276:785-791.
[10] MRC. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;291:97-104.
[11] Pahor M, Psaty BM, Alderman MH et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000;356:1949-1954.

[12] Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. *JAMA* 1997;277:739-745.
[13] Kauffman JM. Aspirin study flawed (letter). *J Scientific Exploration* 2002;16:247-249.
[14] Kronmal A, Hart RG, Manolio TA, et al. Aspirin use and incident stroke in the cardiovascular health study. *Stroke* 1998;29:887-894.
[15] Kauffman JM. Bias in recent papers on diets and drugs in peer-reviewed medical journals. *J Am Phys Surg* 2004;9:11-14.

In Reply: Professor Kauffman unfortunately misses the main point of the article, which is that new therapeutic advances are the way medical costs of cardiovascular disease will be controlled.

LDL cholesterol reduction with statin therapy has consistently reduced cardiovascular events.[1,2] The new technique of intravascular ultrasound (IVUS) now gives us a real-time direct measurement of the lethal clot-forming disease itself in the arterial wall. In the Reversal Study using IVUS to directly measure atheroma size in the arterial wall, there was a 1% reduction in atheroma volume for each 10% reduction in LDL-C level. In some cases, LDL reduction of 50% from baseline reduced atheroma by more than 50%. LDL reduction by statin therapy was clearly associated with control of inflammation (the principal cause of the disease).[2]

The fact that many patients voluntarily stop their therapy is irrelevant in terms of the effectiveness of sustained treatment.

Control of hypertension also reduces cardiovascular events.[3] The Blood Pressure Lowering Treatment Trialists Collaboration (the largest meta-analysis to date of clinical trials on the effects of blood pressure lowering therapies) showed that the relative risk of cardiovascular events was consistently reduced by lowering blood pressure.[4]

Professor Kauffman misinterprets the studies showing a relative risk reduction for beta-blockers. In post-myocardial infarction, the mortality reduction from beta-blockers was unrelated to blood pressure reduction.[5]

Meta-analysis of aspirin therapy also shows consistent reduction in cardiovascular events.[6,7]

We agree that diet has at best a marginal effect. While physical activity is difficult to quantitate, the available evidence shows beneficial effects in reducing the risks of cardiovascular and cerebrovascular disease.[8,9]

Each of these interventions is cumulative.[10] Medical therapy is more effective, less traumatic, and less expensive than current surgically based therapies. The fix for Medicare will be continued technological progress.

J. Philip Smith, M.D.
Karen Cosper, R.N.

[1] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA* 2001;285:2486-2497.
[2] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071-1080.
[3] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC 7 Report. *JAMA* 2003, 289: 2560-2572.
[4] Turnbull F, and the Blood Pressure Lowering treatment Trialists' Collaboration. Effects of different blood-pressure lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet* 2003;362:1527-1535.
[5] Yusuf S, Petro R, Lewis J, et al. Beta blockage during and after myocardial infarction; an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-371.
[6] Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *JAMA* 2004;292:1867-1874.
[7] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
[8] Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990;132:612-628.
[9] Lee IM. Physical activity in women. How much is good enough? *JAMA* 2003;290: 1377-1379.
[10] Yusef S. Two decades of progress in preventing vascular disease. *Lancet* 2002;360:2-3.

MMR Vaccination and Autism

The recent paper by Goldman and Yazbak,[1] claiming to be "an investigation of the association between MMR vaccination and autism in Denmark," is critically flawed in several respects. Because it deals with the Danish population, it has been welcomed by the antivaccination lobby as a direct refutation of the seminal paper by Madsen et al.,[2] whereas in fact it does no such thing.

Goldman and Yazbak do not have data on vaccination status, and therefore cannot compare autism rates between vaccinated and unvaccinated individuals. They rely instead upon demonstrating that the population rate of autism was rising between 1990 and 1992 and therefore, since MMR vaccination was introduced in 1988, MMR vaccination must "logically" be the cause. Correlation, however, is not the same as causation. Studies that have investigated the MMR-autism hypothesis by direct comparisons between vaccinated and unvaccinated individuals have found no evidence of a link.[2,3]

Goldman and Yazbak also attempt to criticise Madsen's study. Their main criticism is that follow-up was not long enough to detect all cases of autism. The MMR-autism hypothesis originally arose from a case series in which the onset of autism came within a few days of vaccination:[4] how can it be plausibly argued that an average follow-up of 4 years was insufficient to test this hypothesis? One of us has written a more detailed critique of their comments elsewhere.[5]

Moreover, their statistical analysis of changes in the prevalence of autism is deeply flawed. By far the greatest increase in the Danish prevalence of autism was from 1994 (when classification systems changed) onwards. Goldman and Yazbak try to use linear regression analysis on only three data points (1990, 1991, and 1992) to estimate the "expected prevalence" of

autism in 2000 as if this classification change had not occurred. Although they also do linear regression on the 1995-2000 data, this does not contribute one whit to their adjusted relative risk, as can be shown with a pocket calculator and their Table 1: the relative risk calculation for autism in 2000 is reached by comparing the 1980-86 rate with the predicted 2000 rate. The so-called "sensitivity analyses" merely explore possible alternative scenarios for different "factors of diagnostic awareness," without examining the error involved in extrapolating 1990-1992 data over the next eight years.

Goldman and Yazbak admit that "the true confidence intervals are wider than indicated because of error associated with linear regression of the trends." As they are kind enough to publish their raw data, we were able to calculate the confidence intervals associated with the linear regression. The predicted prevalence per 100,000 in 2000 based on the regression of the 1990-1992 data – on which the whole analysis depends – is 39.42, but with a 95% confidence interval of -3.57 to 82.6. Astute readers will notice that a negative value for prevalence is nonsensical, but this is simply a function of Goldman and Yazbak's inappropriate statistical model: a Poisson model would have been more appropriate.

Nonetheless, the main point is that their data do not show a significant increase in the prevalence of autism at all, other than that owing to "greater diagnostic awareness."

Matthew L. Grove, B.Sc., M.B.B.S., M.R.C.P.
Consultant Rheumatologist
North Tyneside General Hospital
Rake Lane, North Shields, Tyne & Wear
NE29 8NH, UK

Adam Jacobs, Ph.D., M.Sc.
Director, Dianthus Medical Limited
Lombard Business Park, 8 Lombard Road
London, SW19 3TZ, UK

Conflict of interest statement: MLG accepted funding from Wyeth once in the past to attend a conference, and has been paid a speaker's fee (once) to talk on osteoporosis by Lilly. Both companies have made vaccines in the past, although MLG has had no involvement with any vaccine program of any kind. AJ's company regularly provides consultancy services to a variety of pharmaceutical companies, some of which make vaccines, including SmithKline Beecham and Aventis-Pasteur.

[1] Goldman GS, Yazbak FE. An investigation of the association between MMR vaccination and autism in Denmark. *J Am Phys Surg* 2004;9(3):70-75.

[2] Madsen KE, Hviid A, Vestergaard M., et al. A population-based study of measles, mumps, and rubella vaccination and autism. *N Eng J Med* 2002;347:1477-1482.

[3] Smeeth L, Cook C, Fombonne E. MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004;364:963-969.

[4] Wakefield AJ, Murch SH, Anthony A. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:637-41

[5] Jacobs A. Re: Re: Have vicars-general of vaccination got the needle? BMJ Rapid Responses, Oct. 5, 2004. Available at: http://bmj.bmjjournals.com/cgi/eletters/325/7373/1134/a#77105. Accessed Nov. 3, 2004.

In Reply: We have candidly disclosed the limitations of our study, which were also discussed by Stott et al.[1] While carefully listing the confounding factors, we have clearly shown that the prevalence of autism did indeed increase in Denmark after the introduction of MMR vaccination. So have Stott et al. Indeed, so has Madsen himself in a study in *Pediatrics,*[2] just ten months after his publication in the *New England Journal of Medicine:*[3] "From 1991 until 2000 the incidence increased and continued to rise after the removal of thimerosal from vaccines." Children born after the introduction of the MMR turned 4 in 1991 and were old enough to be diagnosed. In fact, Madsen's data when stratified by age also support an MMR-autism association.[1]

Grove and Jacobs confuse the onset of autistic symptoms, which can indeed occur shortly after MMR vaccination, with the diagnosis of autism, which is reached in Denmark around age 5. Indeed professional help is often first sought months after initial parental concerns.[4]

The vaccination status of children in the Madsen study was discussed in the Stott paper, in which S. Suissa, Professor of Epidemiology, Biostatistics and Medicine at McGill University, was quoted as stating:

> Madsen et al. observe an adjusted rate ratio of autistic disorder after vaccination of 0.92 relative to no vaccination, when the crude rate ratio (my computation) was 1.45 (95% confidence interval 1.08-1.95). Moreover, the rate by time since vaccination increases to a high of 27.3 two years after vaccination (rate ratio 2.5) and decreases thereafter to 11.4 per 100,000 per year.

Grove and Jacobs fail to recognize that prior to performing the linear extrapolation, a statistically significant increase in annual autism had occurred: from 7.8 per 100,000 in 1990 to 14.1 per 100,000 in 1992 among children 5 to 9 years old. Using 325,000 (or 5 x 65,000) as the number of children in this cohort (based on a birth cohort of 65,000), we have a statistically significant (at a 97.5% level) increase from 25 cases per 325,000 children (or 7.8/100,000) in 1990 to 46 cases per 325,000 children (or 14.1/100,000) in 1992, χ^2=6.21 (P<0.025, 1-degree of freedom). Thus, the annual incidence rate in 1992 was already higher than the minimum 12.9 per 100,000 required for statistical significance. The ratio of the 1992 to 1990 rates is statistically significant, yielding a risk of 1.8 (95% CI, 1.1 to 2.9, based on the Poisson distribution). Since the confidence interval does not include 1, a statistically significant effect is demonstrated.

While we agree that the confidence interval is large when data are extrapolated to 2000, a statistically significant increase in annual autism cases (or prevalence) had already occurred from 1990 to 1992, prior to the subsequent changes in both classification and inpatient/outpatient enrollments. We saw the extrapolation as a novel way of estimating a cumulative (1990 to 2000) percentage increase in autism by avoiding influence of the confounders, which were previously promoted as qualitative reasons for the autism increase to avoid the possible implication of MMR vaccination. If autism cases were arising as a consequence of MMR vaccination, we would expect a

linear increase in autism each successive year as vaccinees entered the 5- to 9-year-old cohort. Thus, it was not unreasonable to use a linear relationship from 1990-1992 with high correlation (98.5%) to extrapolate the expected cases in 2000.

Gary S. Goldman, Ph.D.
F. Edward Yazbak, MD, F.A.A.P.

[1] Stott C, Blaxill M, Wakefield AJ. MMR and Autism in perspective: the Denmark story. *J Am Phys Surg* 2004:9:89-92

[2] Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3 Pt 1):604-6.

[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;347:1477-82.

[4] De Giacomo A, Fombonne E. Parental recognition of developmental abnormalities in autism. *Eur Child Adolesc Psychiatry* 1998;7:131-6.

More on Madsen's Analysis

The 2003 study of Madsen et al. (cited above), one of the works that the Institute of Medicine's Vaccine Safety Review Committee has deemed "well-designed," has been used in an attempt to refute a thimerosal-autism connection,[1] as well as an MMR-autism connection.

As the studies cited above by Goldman and Yazbak and Stott et al. pointed out, Madsen's findings may have been skewed by participant selection and changes in diagnostic groupings.

Madsen's collection of inpatient treatment data since 1971 was tainted by adding outpatient activities after 1994. Madsen et al. attempt to reconcile this disparity by writing: "In additional analyses we examined data using inpatients only...to elucidate the contribution of the outpatient registration to the change in incidence. The same trend with an increase in the incidence rates from 1990 until the end of the study period was seen." They also write that "[t]he proportion of outpatient to inpatient activities was about 4 to 6 times as many outpatients as inpatients…" Yet in the 2002 publication (cited above), Madsen et al. use the same data to assert: "In our cohort, 93.1% of the children were treated only as outpatients.…"

This creates a huge disparity between the two studies, which reportedly used the same data. One study claims "4 to 6 times as many outpatients as inpatients," yet the proportion of 93.1% outpatients and 6.9% inpatients yields a ratio in excess of 13.5:1. Despite the authors' claim that the outpatient registration did not substantively change the incidence in autism, it is easily seen, by making an adjustment for the more valid claim of 13.5:1 ratio, that the original assertion of a statistically valid upward trend can be completely explained by the difference in accounting for cohorts before and after 1995.

Regarding diagnostic categories, the authors write, in 2003: "The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantilis (International Classification of Diseases, Eighth Revision [ICD-8]: 299.00) or psychosis infantilis posterior (ICD-8: 299.01) or from 1994 onward, infantile autism… (ICD-10: F84.0) or atypical autism (ICD-10: F84.1)."

Although the authors do not fully address the effect of this change, data presented in Figure 1 of the 2003 Madsen study show that the autism incidence before 1994 is on average approximately 6/10,000 patients (derived by summing the incidence data for each of the three age groups presented and accounting for the 13.5 to 1 ratio of outpatients to inpatients).

In contrast, the 2002 Madsen study reports autism incidence between 1.2/10,000 (DSM-IV/ICD-8 criteria) to 30.8/10,000 (ICD-10 criteria). The earliest available study on the incidence of autism in Denmark[2] reports an intermediate value of 4/10,000, presumably using the ICD-8 criteria, which is in line with the 2003 Madsen study's pre-1994 average.

Thus, using the pre-1992 ICD-8 psychosis infantilis incidence derived from the 2003 Madsen study (6/10000), the ICD-10/ICD-8 diagnosis ratio is at least 5:1 (i.e., 30.8 divided by 6) and may be as high as 25:1 (30.8 divided by 1.2).

Other authors write: "Prior to 1992, the data in the [Danish] national register did not include cases diagnosed in one large clinic in Copenhagen (which accounts for approximately 20% of cases occurring nationwide)."[3] This presumably means that all data points up to 1992 should be multiplied by 1.2 to correct for this discrepancy.

Because of these difficulties, the 2003 Madsen analysis is at best indeterminate regarding the effect of discontinuing the use of thimerosal-containing vaccines on autism incidence. It is apparent that the upward trend reported in the 2003 Madsen study may be fully attributed to a overwhelmingly faulty bias caused by (1) switching accounting from inpatient to outpatient records in 1995; (2) gross disparities in ICD-8 and ICD-10 diagnoses used up to, through, and after 1994 and (3) the inclusion of the Copenhagen clinic in 1993, thus increasing cohorts at that point onward by an estimated 20%. Further, contrary to the study authors' conclusions, using factors discussed above to correct for inaccuracies in the 2003 Madsen study, we find significant decreases in autism incidence after 1993 among each group studied, including a dramatic 75% reduction within the 2 to 4-year-old cohort.

It is curious that the study authors chose to include these confounders when 2 of the 3 (i.e., inpatient/outpatient accounting and inclusion of patients from the Copenhagen clinic) could have been easily avoided through proper accounting of the existing data in the Danish registry. Numerous other questions that arise from reanalyzing Madsen's data are beyond the scope of a letter to the editor.

Jeffrey Allen Trelka
Brian S. Hooker, Ph.D., P.E.

Disclosures: Both authors are Research Scientists with the Autism Healing Network and both are parents of autistic children. No financial conflicts were disclosed.

[1] Institute of Medicine (US). *Immunization Safety Review: Vaccines and Autism*. Washington, D.C.: National Academy Press; 2004.

[2] Brask BM. A prevalence investigation of childhood psychoses. In: Nordic Symposium on the Comprehensive Care of the Psychotic Children. Oslo, Norway: Barnpsykiatrist Forening; 1972:145-153.

[3] Stehr-Green P, Tull P, Stellfeld M, Mortensen PB, Simpson D. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med* 2003;25:101-106.