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CITATIONS FROM THE VACCINE-FRIENDLY PLAN

Dr. Paul's Safe and Effective Approach to Immunity and Health - from Pregnancy Through Your Child's Teen Years

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CHAPTER 1

A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning.

Abstract

BACKGROUND:
Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

METHODS:
We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

RESULTS:
The 90 infants who received the standard feeding solutions had a mean (+/-SD) Bayley Mental Development Index of 95+/-22, as compared with 98+/-20 for the 92 infants who received the aluminum-depleted solutions (P=0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92+/-20 and 102+/-17, respectively (P=0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P=0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P=0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

CONCLUSIONS:
In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development.

Citation:
Roberts, Darren M., Nick A. Buckley, Fahim Mohamed, Michael Eddleston, Daniel A. Goldstein, Akbar Mehrsheikh, Marian S. Bleeke, and Andrew H. Dawson. "A Prospective Observational Study of the Clinical Toxicology of Glyphosate-containing Herbicides in Adults with Acute Self-poisoning." Clinical Toxicology 48.2 (2010): 129-36. http://www.ncbi.nlm.nih.gov/pubmed/20136481

Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders.

Abstract

IMPORTANCE:
Acetaminophen (paracetamol) is the most commonly used medication for pain and fever during pregnancy in many countries. Research data suggest that acetaminophen is a hormone disruptor, and abnormal hormonal exposures in pregnancy may influence fetal brain development.

OBJECTIVE:
To evaluate whether prenatal exposure to acetaminophen increases the risk for developing attention-deficit/hyperactivity disorder (ADHD)-like behavioral problems or hyperkinetic disorders (HKDs) in children.

DESIGN, SETTING, AND PARTICIPANTS:
We studied 64,322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002.

EXPOSURES:
Acetaminophen use during pregnancy was assessed prospectively via 3 computer-assisted telephone interviews during pregnancy and 6 months after child birth.

MAIN OUTCOMES AND MEASURES:
To ascertain outcome information we used (1) parental reports of behavioral problems in children 7 years of age using the Strengths and Difficulties Questionnaire; (2) retrieved HKD diagnoses from the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and (3) identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry.

We estimated hazard ratios for receiving an HKD diagnosis or using ADHD medications and risk ratios for behavioral problems in children after prenatal exposure to acetaminophen.

RESULTS:
More than half of all mothers reported acetaminophen use while pregnant. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes (ie, HKD diagnosis, ADHD medication use, and ADHD-like behaviors; P trend < .001). Results did not appear to be confounded by maternal inflammation, infection during pregnancy, the mother's mental health problems, or other potential confounders we evaluated.

CONCLUSIONS AND RELEVANCE:
Maternal acetaminophen use during pregnancy is associated with a higher risk for HKDs and ADHD-like behaviors in children. Because the exposure and outcome are frequent, these results are of public health relevance but further investigations are needed.

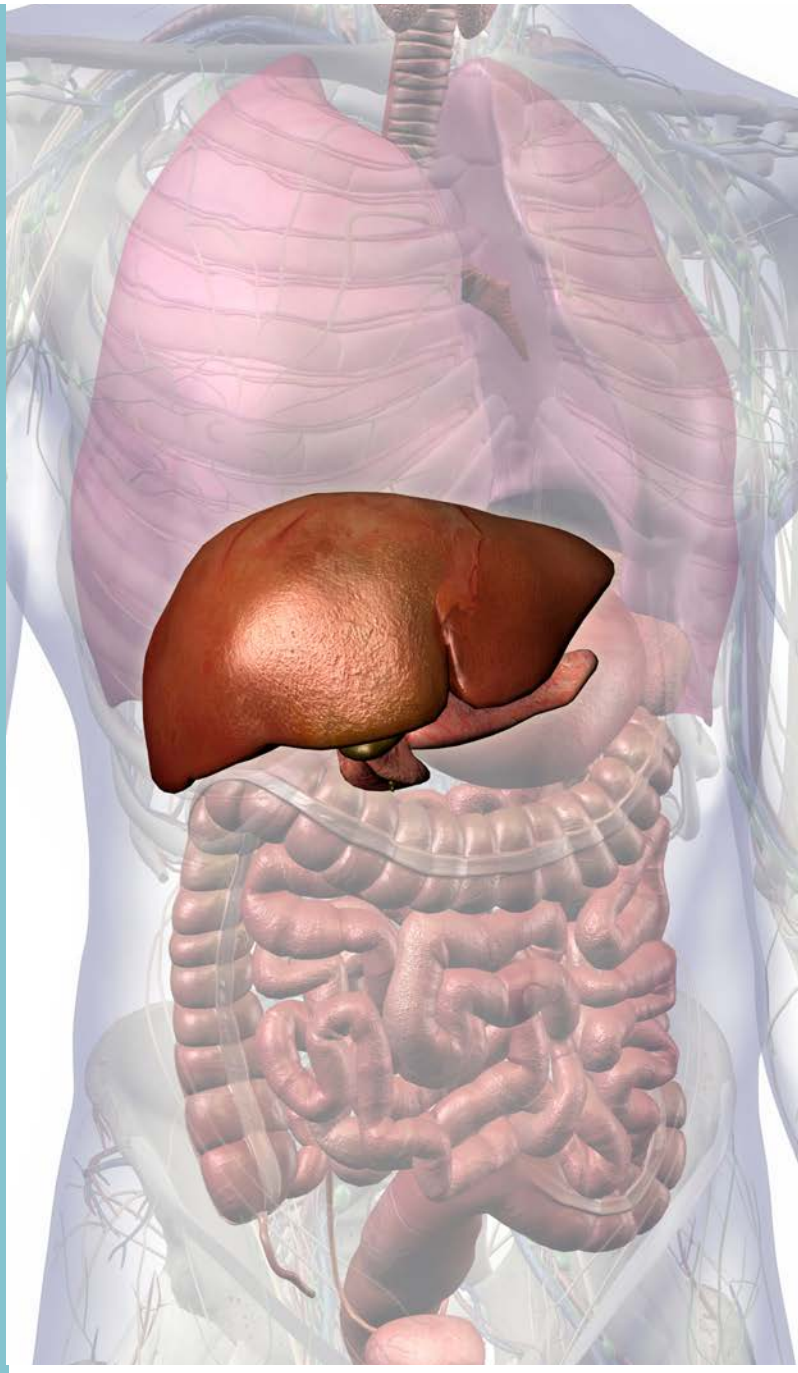
Citation:
Liew, Zeyan, Beate Ritz, Cristina Rebordosa, Pei-Chen Lee, and Jørn Olsen. "Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders." JAMA Pediatrics JAMA Pediatr 168.4 (2014): 313. https://pubmed.ncbi.nlm.nih.gov/24566677/

Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study

Abstract

Severe acetaminophen hepatotoxicity frequently leads to acute liver failure (ALF). We determined the incidence, risk factors, and outcomes of acetaminophen-induced ALF at 22 tertiary care centers in the United States. Detailed prospective data were gathered on 662 consecutive patients over a 6-year period fulfilling standard criteria for ALF (coagulopathy and encephalopathy), from which 275 (42%) were determined to result from acetaminophen liver injury. The annual percentage of acetaminophen-related ALF rose during the study from 28% in 1998 to 51% in 2003. Median dose ingested was 24 g (equivalent to 48 extra-strength tablets). Unintentional overdoses accounted for 131 (48%) cases, intentional (suicide attempts) 122 (44%), and 22 (8%) were of unknown intent. In the unintentional group, 38% took two or more acetaminophen preparations simultaneously, and 63% used narcotic-containing compounds. Eighty-one percent of unintentional patients reported taking acetaminophen and/or other analgesics for acute or chronic pain syndromes. Overall, 178 subjects (65%) survived, 74 (27%) died without transplantation, and 23 subjects (8%) underwent liver transplantation; 71% were alive at 3 weeks. Transplant-free survival rate and rate of liver transplantation were similar between intentional and unintentional groups.

In conclusion, acetaminophen hepatotoxicity far exceeds other causes of acute liver failure in the United States. Susceptible patients have concomitant depression, chronic pain, alcohol or narcotic use, and/or take several preparations simultaneously. Education of patients, physicians, and pharmacies to limit high-risk use settings is recommended.



Citation:
Holubek, William J., Susanne Kalman, and Robert S. Hoffman. "Acetaminophen-induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study." Hepatology 43.4 (2006): 880. https://pubmed.ncbi.nlm.nih.gov/16317692/

Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions

Abstract

BACKGROUND:
Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

METHODS:
We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

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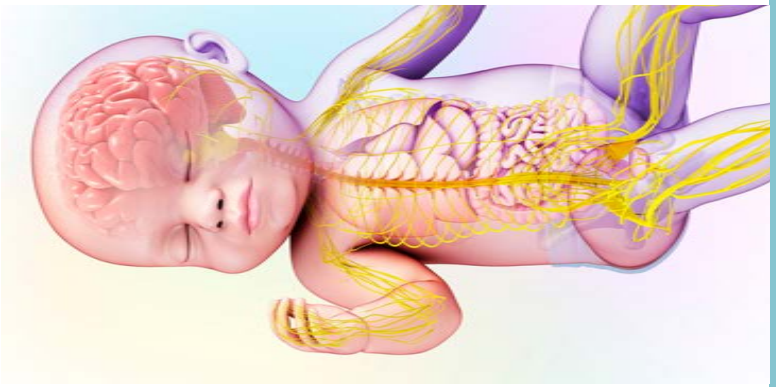
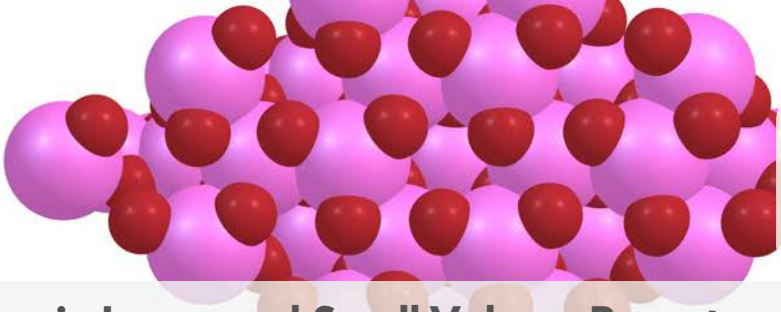
The 90 infants who received the standard feeding solutions had a mean (+/-SD) Bayley Mental Development Index of 95+/-22, as compared with 98+/-20 for the 92 infants who received the aluminum-depleted solutions (P=0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92+/-20 and 102+/-17, respectively (P=0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P=0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P=0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

CONCLUSIONS:
In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development.



Citation:
Bishop, Nicholas J., Ruth Morley, J. Philip Day, and Alan Lucas. "Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions." New England Journal of Medicine N Engl J Med 336.22 (1997): 1557-562. https://pubmed.ncbi.nlm.nih.gov/9164811/



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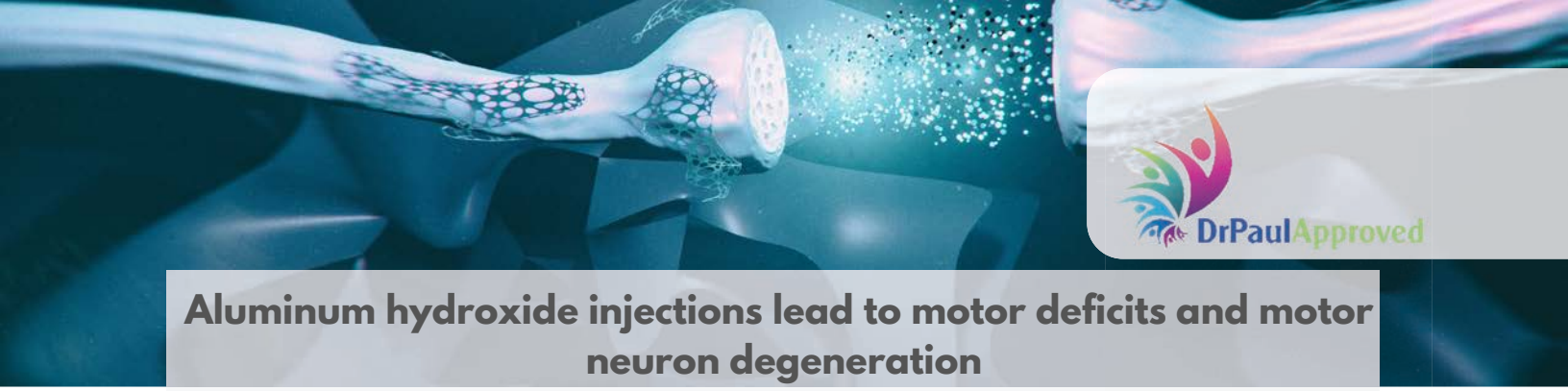
Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date

Abstract

The Food and Drug Administration (FDA) is delaying until January 26, 2003, the effective date of a final rule published in the Federal Register of January 26, 2000 (65 FR 4103), and originally scheduled to become effective on January 26, 2001. The final rule amends FDA's regulations to add certain labeling requirements for aluminum content in large volume parenterals (LVP's), small volume parenterals (SVP's), and pharmacy bulk packages (PBP's) used in total parenteral nutrition (TPN). The rule also specifies an upper limit of aluminum permitted in LVP's and requires applicants to submit to FDA validated assay methods for determining aluminum content in parenteral drug products. FDA is delaying the effective date of this rule to address concerns raised by affected parties about the possible inability to meet the requirements of the rule by the current effective date.

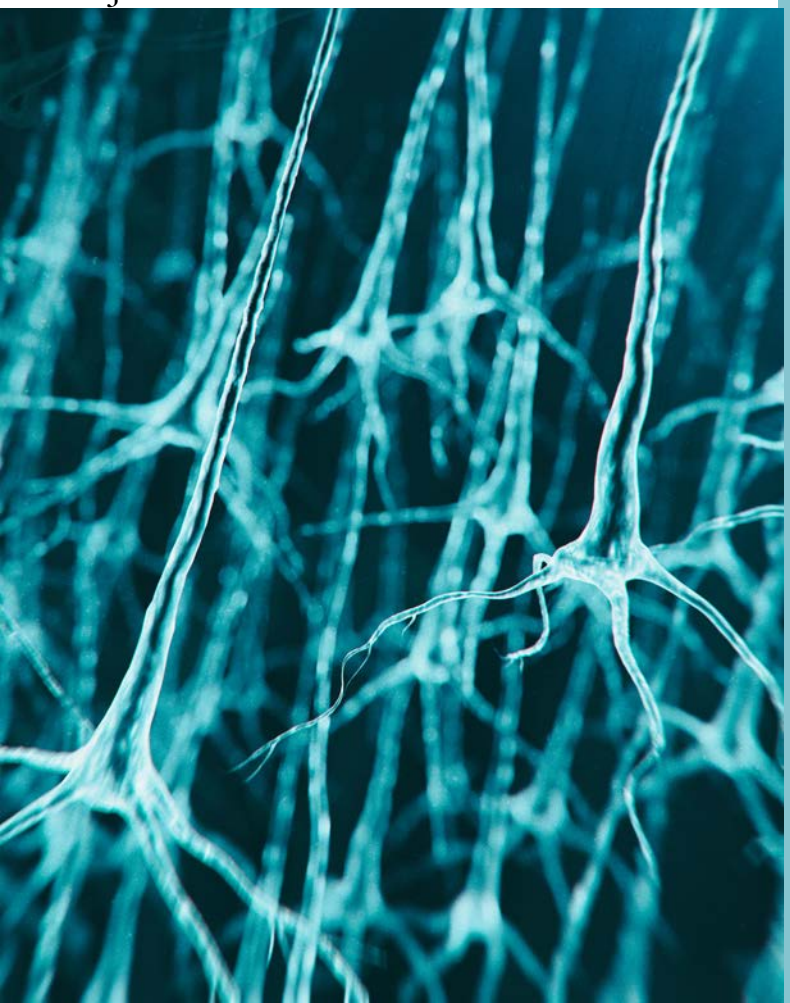
Citation:
Food and Drug Administration. "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Delay of Effective Date." Federal Register. N.p., 26 Jan. 2001.
https://www.federalregister.gov/documents/2001/01/26/01-2125/aluminum-in-large-and-small-volume-parenterals-used-in-total-parenteral-nutrition-delay-of-effective



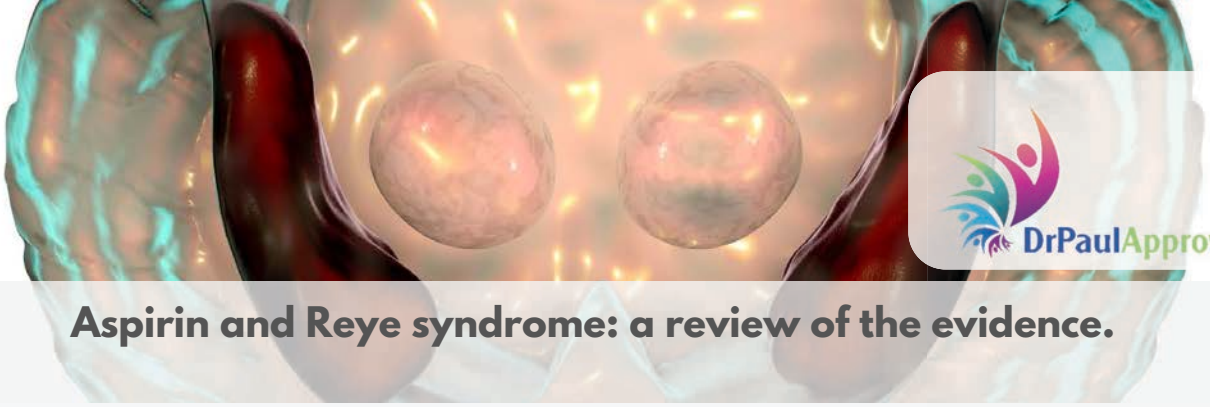
Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration

Abstract

Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS "cluster" represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. The demonstrated neurotoxicity of aluminum hydroxide and its relative ubiquity as an adjuvant suggest that greater scrutiny by the scientific community is warranted.



Citations:
Shaw, Christopher A., and Michael S. Petrik. "Aluminum Hydroxide Injections Lead to Motor Deficits and Motor Neuron Degeneration." Journal of Inorganic Biochemistry 103.11 (2009): 1555-562.
https://pubmed.ncbi.nlm.nih.gov/19740540/



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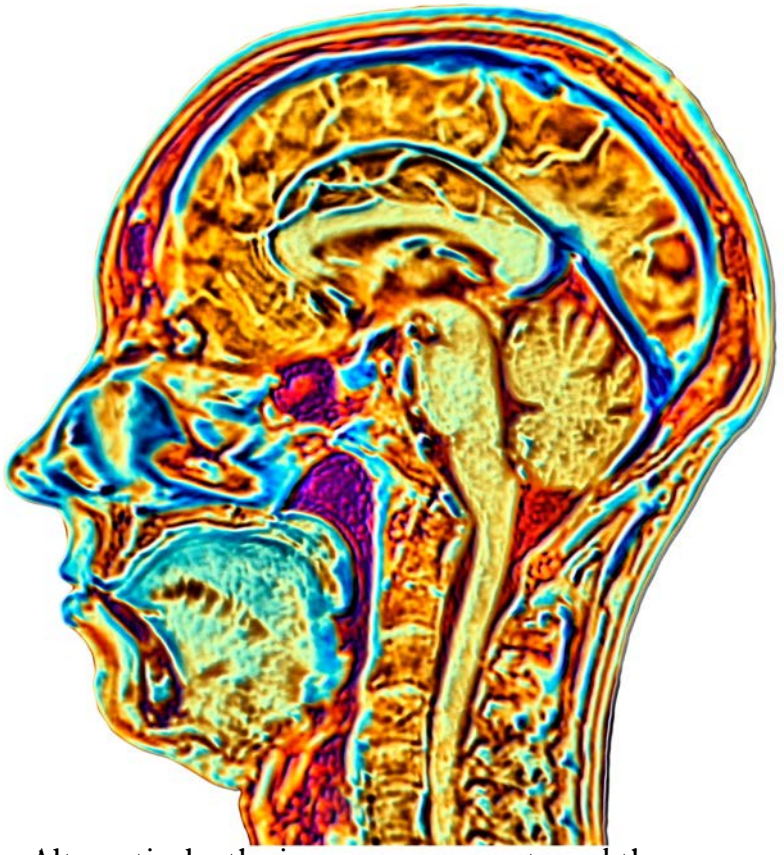
Aspirin and Reye syndrome: a review of the evidence.

Abstract

Reye syndrome is an extremely rare but severe and often fatal disease. Death occurs in about 30-40% of cases from brainstem dysfunction. The disease typically is preceded by a viral infection with an intermediate disease-free interval of 3-5 days. The biochemical explanation for Reye-like symptoms is a generalized disturbance in mitochondrial metabolism, eventually resulting in metabolic failure in the liver and other tissues. The etiology of 'classical' Reye syndrome is unknown. Hypothetically, the syndrome may result from an unusual response to the preceding viral infection, which is determined by host genetic factors but can be modified by a variety of exogenous agents. Thus, several infections and diseases might present clinically with Reye-like symptoms. Exogenous agents involve a number of toxins, drugs (including aspirin [acetylsalicylic acid]), and other chemicals. The 'rise and fall' in the incidence of Reye syndrome is still poorly understood and unexplained. With a few exceptions, there were probably no new Reye-like diseases reported during the last 10 years that could not be explained by an inherited disorder of metabolism or a misdiagnosis. This may reflect scientific progress in the better understanding of cellular and molecular dysfunctions as disease-determining factors.



Alternatively, the immune response to and the virulence of a virus might have changed by alteration of its genetic code. The suggestion of a defined cause-effect relationship between aspirin intake and Reye syndrome in children is not supported by sufficient facts. Clearly, no drug treatment is without side effects. Thus, a balanced view of whether treatment with a certain drug is justified in terms of the benefit/risk ratio is always necessary. Aspirin is no exception.

Citations:
Schrör, Karsten. "Aspirin and Reye Syndrome." Pediatric Drugs 9.3 (2007): 195-204.
https://pubmed.ncbi.nlm.nih.gov/17523700/

Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks.

Abstract

OBJECTIVE:
To study the efficacy and tolerability of 1 g of intravenous magnesium sulfate as acute treatment of moderate or severe migraine attacks.

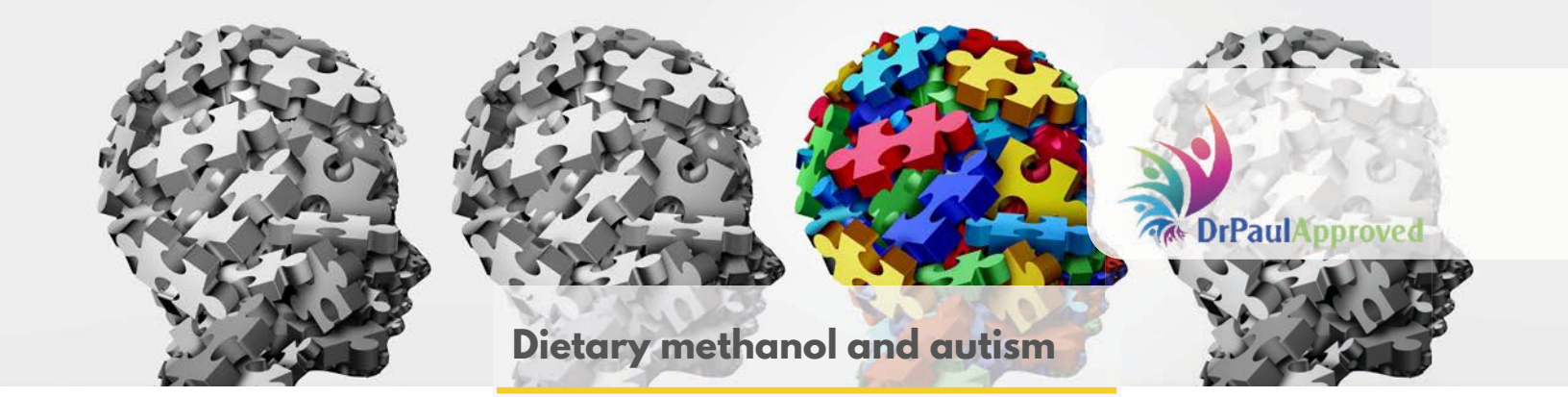
BACKGROUND:
Migraine is a common disorder in which not only the pain but also the accompanying symptoms such as nausea and vomiting reduce activity and productivity of sufferers. Many drugs used for the treatment of acute migraine attacks have many side effects, are not well tolerated, are ineffective in some patients, or cannot be used during pregnancy or in patients with ischemic heart disease. Magnesium deficiency has been proposed to play a role in the pathophysiology of migraine, and recently treatment of migraine with magnesium has gained considerable interest.

METHODS:
This was a randomized, single-blind, placebo-controlled trial including 30 patients with moderate or severe migraine attacks. Fifteen patients received 1 g intravenous magnesium sulfate given over 15 minutes. The next 15 patients received 10 mL of 0.9% saline intravenously. Those in the placebo group with persisting complaints of pain or nausea and vomiting after 30 minutes also received 1 g magnesium sulfate intravenously over 15 minutes. The patients were assessed immediately after treatment, and then 30 minutes and 2 hours later. Intensity of pain, accompanying symptoms, and side effects were noted.

RESULTS:
All patients in the treatment group responded to treatment with magnesium sulfate. The pain disappeared in 13 patients (86.6%); it was diminished in 2 patients (13.4%); and in all 15 patients (100%), accompanying symptoms disappeared. In the placebo group, a decrease in pain severity but persisting nausea, irritability, and photophobia were noted in 1 patient (6.6%). Accompanying symptoms disappeared in 3 patients (20%) 30 minutes after placebo administration. All patients initially receiving placebo were subsequently given magnesium sulfate. All of these patients responded to magnesium sulfate. In 14 patients (93.3%), the attack ended; in 1 patient (6.6%), pain intensity decreased; and in all 15 patients (100%), accompanying symptoms disappeared. Both the response rate (100% for magnesium sulfate and 7% for placebo) and the pain-free rate (87% for magnesium sulfate and 0% for placebo) showed that magnesium sulfate was superior to placebo. Twenty-six patients (86.6%) had mild side effects which did not necessitate discontinuing treatment during magnesium sulfate administration.

CONCLUSION:
Our results show that 1 g intravenous magnesium sulfate is an efficient, safe, and well-tolerated drug in the treatment of migraine attacks. It is possible that magnesium sulfate could be used in a broader spectrum of patients than other drugs commonly used for attack treatment. In view of these results, the effect of magnesium sulfate in acute migraine should be examined in large scale studies

Citation:
Demirkaya, Seref, Okay Vural, Babur Dora, and Mehmet Akif Topcuoglu. "Efficacy of Intravenous Magnesium Sulfate in the Treatment of Acute Migraine Attacks." Headache Headache: The Journal of Head and Face Pain 41.2 (2001): 171-77.
https://pubmed.ncbi.nlm.nih.gov/11251702/



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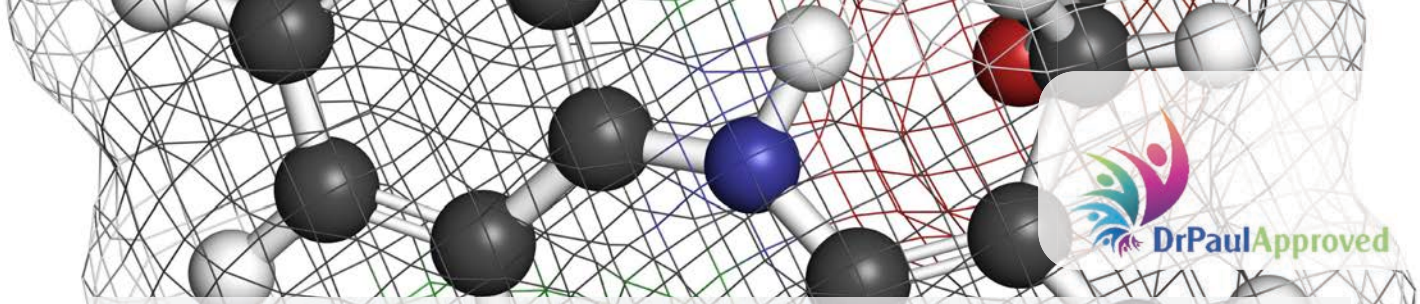
Dietary methanol and autism

Abstract

The authors sought to establish whether maternal dietary methanol during pregnancy was a factor in the etiology of autism spectrum disorders. A seven item questionnaire was given to women who had given birth to at least one child after 1984. The subjects were solicited from a large primary care practice and several internet sites and separated into two groups – mothers who had given birth to a child with autism and those who had not. Average weekly methanol consumption was calculated based on questionnaire responses. 550 questionnaires were completed by women who gave birth to a non-autistic child. On average these women consumed 66.71 mg. of methanol weekly. 161 questionnaires were completed by women who had given birth to an autistic child. The average estimated weekly methanol consumption for this group was 142.31 mg. Based on the results of the Wilcoxon rank sum-test, we see a significant difference between the reported methanol consumption rates of the two groups. This study suggests that women who have given birth to an autistic child are likely to have had higher intake of dietary sources of methanol than women who had given birth to an autistic child.

Citation:
Walton, Ralph G., and Woodrow C. Monte. "Dietary Methanol and Autism." Medical Hypotheses 85.4 (2015): 441-46.
https://www.sciencedirect.com/science/article/pii/S0306987715002443



Intestinal permeability and inflammation in patients on NSAIDs

Abstract

BACKGROUND:
The frequency with which non-steroidal anti-inflammatory drugs (NSAIDs) increase small intestinal permeability and cause inflammation is uncertain.

AIMS:
To examine small intestinal permeability and inflammation in a large number of patients on long term NSAIDs.

METHODS:
Sixty eight patients receiving six different NSAIDs for over six months underwent combined absorption-permeability tests at three different test dose osmolarities (iso-, hypo-, and hyperosmolar). Two hundred and eighty six patients on 12 different NSAIDs underwent indium111 white cell faecal excretion studies to assess the prevalence and severity of intestinal inflammation.

RESULTS:
The iso- and hyperosmolar tests showed significant malabsorption of 3-o-methyl-D-glucose, Dxylose, and L-rhamnose. Intestinal permeability changes were significantly more pronounced and frequent with the hypo- and hyperosmolar as opposed to the iso-osmolar test. Sequential studies showed that four and nine patients (of 13) developed inflammation after three and six months treatment with NSAIDs, respectively. There was no significant difference ($p>0.1$) in the prevalence (54-72%) or severity of intestinal inflammation in the 286 patients taking the various NSAIDs apart from those on aspirin and nabumetone, these having no evidence of intestinal inflammation. There was no significant correlation between the inflammatory changes and age, sex, dose of NSAID, length of disease, or NSAID ingestion.

Conclusions
Intestinal permeability test dose composition is an important factor when assessing the effects of NSAIDs on intestinal integrity. All the conventional NSAIDs studied were equally associated with small intestinal inflammation apart from aspirin and nabumetone which seem to spare the small bowel.

Citation:
Sigthorsson, G., J. Tibble, J. Hayllar, I. Menzies, A. Macpherson, R. Moots, D. Scott, M. J. Gumpel, and I. Bjarnason. "Intestinal Permeability and Inflammation in Patients on NSAIDs." Gut 43.4 (1998): 506-11.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1727292/

Longitudinal analysis of the association between removal of dental amalgam, urine mercury and 14 self-reported health symptoms

Abstract

BACKGROUND:

Mercury vapor poses a known health risk with no clearly established safe level of exposure. Consequently there is debate over whether the level of prolonged exposure to mercury vapor from dental amalgam fillings, combining approximately 50% mercury with other metals, is sufficiently high to represent a risk to health. The objective of our study is to determine if mercury exposure from amalgam fillings is associated with risk of adverse health effects.

METHODS:

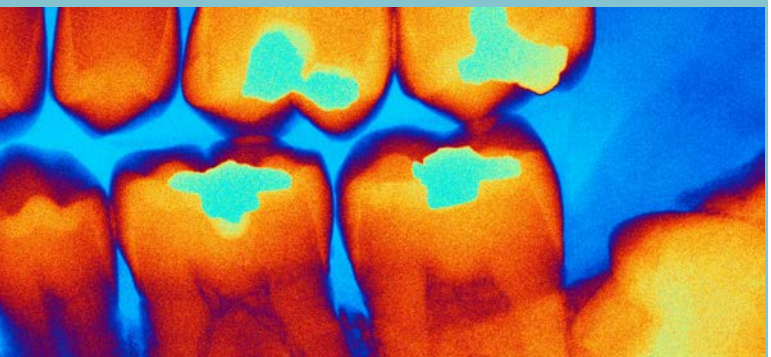
In a large longitudinal non-blind sample of participants from a preventative health program in Calgary, Canada we compared number of amalgam fillings, urine mercury measures and changes in 14 self-reported health symptoms, proposed to be mercury dependent sub-clinical measures of mental and physical health. The likelihood of change over one year in a sample of persons who had their fillings removed was compared to a sample of persons who had not had their fillings removed. We use non-parametric statistical tests to determine if differences in urine mercury were statistically significant between sample groups. Logistic regression models were used to estimate the likelihood of observing symptom improvement or worsening in the sample groups.

RESULTS:

At baseline, individuals with dental amalgam fillings have double the measured urine mercury compared to a control group of persons who have never had amalgam fillings. Removal of amalgam fillings decreases measured urine mercury to levels in persons without amalgam fillings. Although urine mercury levels in our sample are considered by Health Canada to be too low to pose health risks, removal of amalgam fillings reduced the likelihood of self-reported symptom deterioration and increased the likelihood of symptom improvement in comparison to people who retained their amalgam fillings.

CONCLUSIONS:

Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk. The use of safer alternative materials for dental fillings should be encouraged to avoid the increased risk of health deterioration associated with unnecessary exposure to mercury.



Citation:

Zwicker, Jennifer D., Daniel J. Dutton, and John Charles Herbert Emery. "Longitudinal Analysis of the Association between Removal of Dental Amalgam, Urine Mercury and 14 Self-reported Health Symptoms." Environmental Health Environ Health 13.1 (2014)

https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-13-95

Mercury Exposure and Antinuclear Antibodies among Females of Reproductive Age in the United States: NHANES

Abstract

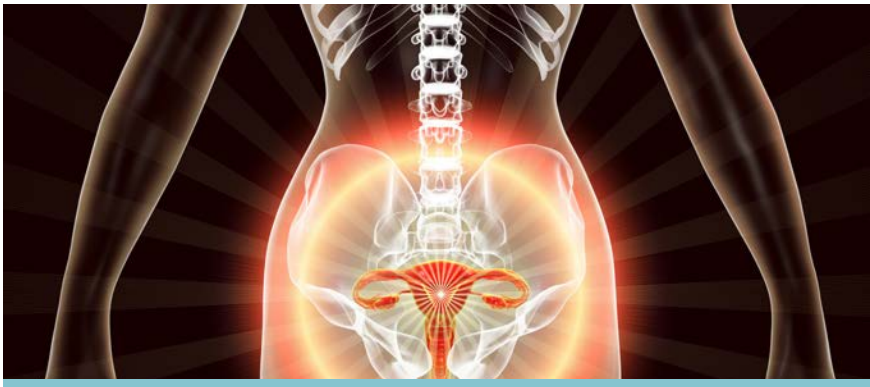
BACKGROUND:
Immune dysregulation associated with mercury has been suggested, although data in the general population are lacking. Chronic exposure to low levels of methylmercury (organic) and inorganic mercury is common, such as through fish consumption and dental amalgams.

OBJECTIVE:
We examined associations between mercury biomarkers and antinuclear antibody (ANA) positivity and titer strength.

METHODS:
Among females 16–49 years of age (n = 1,352) from the National Health and Nutrition Examination Survey (NHANES) 1999–2004, we examined cross-sectional associations between mercury and ANAs (indirect immunofluore-scence; cutoff ⩾ 1:80). Three biomarkers of mercury exposure were used: hair (available 1999–2000) and total blood (1999–2004) predominantly represented methylmercury, and urine (1999–2002) represented inorganic mercury. Survey statistics were used. Multivariable modeling adjusted for several covariates, including age and omega-3 fatty acids.

RESULTS:
Sixteen percent of females were ANA positive; 96% of ANA positives had a nuclear speckled staining pattern. Geometric mean (geometric SD) mercury concentrations were 0.22 (0.03) ppm in hair, 0.92 (0.05) μg/L blood, and 0.62 (0.04) μg/L urine. Hair and blood, but not urinary, mercury were associated with ANA positivity (sample sizes 452, 1,352, and 804, respectively), after adjusting for confounders: for hair, odds ratio (OR) = 4.10 (95% CI: 1.66, 10.13); for blood, OR = 2.32 (95% CI: 1.07, 5.03) comparing highest versus lowest quantiles. Magnitudes of association were strongest for high-titer (⩾ 1:1,280) ANA: hair, OR = 11.41 (95% CI: 1.60, 81.23); blood, OR = 5.93 (95% CI: 1.57, 22.47).

CONCLUSIONS:
Methylmercury, at low levels generally considered safe, was associated with subclinical autoimmunity among reproductive-age females. Autoantibodies may predate clinical disease by years; thus, methylmercury exposure may be relevant to future autoimmune disease risk.



Citation:
Somers, Emily C., Martha A. Ganser, Jeffrey S. Warren, Niladri Basu, Lu Wang, Suzanna M. Zick, and Sung Kyun Park. "Mercury Exposure and Antinuclear Antibodies among Females of Reproductive Age in the United States: NHANES."Environ Health Perspect Environmental Health Perspectives (2015) https://ehp.niehs.nih.gov/doi/10.1289/ehp.1408751

Methanol, formaldehyde, and sodium formate exposure in rat and mouse conceptuses: a potential role of the visceral yolk sac in embryotoxicity.

Abstract

BACKGROUND:
Methanol (CH_3OH) is believed to be teratogenic based on rodent studies. The mouse is more sensitive than the rat, but mechanisms of toxicity and identification of teratogenic metabolites are uncertain.

METHODS:
Rat and mouse whole embryo cultures are used to distinguish toxicity of CH_3OH and its metabolites, formaldehyde (HCHO) and formate (HCOONa), which are produced following transit through the visceral yolk sac (VYS), via addition to culture medium, or by direct embryonic exposure through microinjection into the amnion.

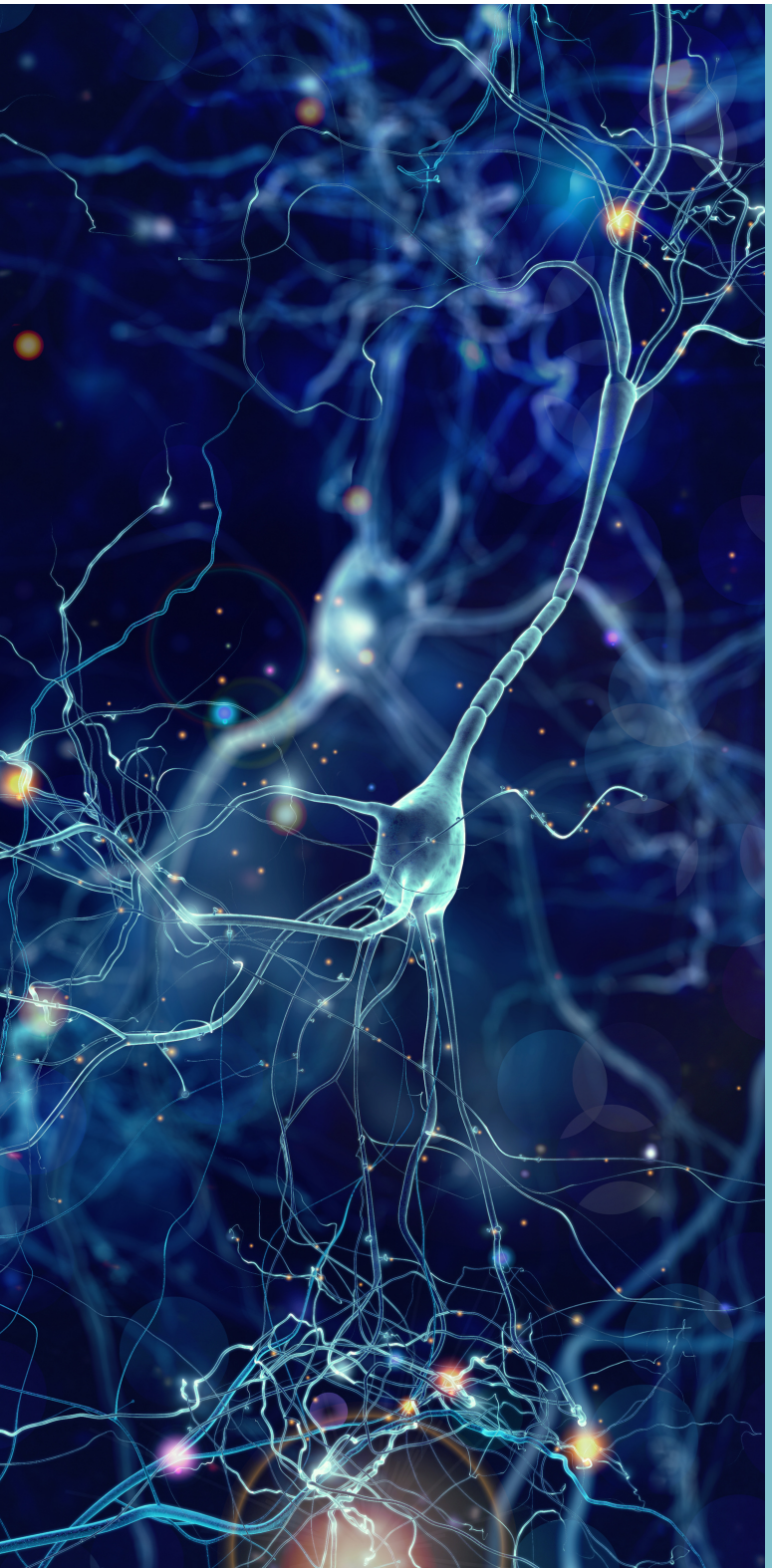
RESULTS:
Embryonic viability, increased dysmorphogenesis, and decreased growth parameters were altered in a dose-dependent fashion for each compound. Mouse embryos were more sensitive than rat, as indicated by significant decreases in viability at comparable, lower concentrations. HCHO produced dysmorphogenesis and caused embryolethality at nearly 1000-fold lower concentrations (0.004 mg/ml) than seen with either CH_3OH or HCOONa. All agents produced incomplete axial rotation and delayed neural tube closure in mice, but only CH_3OH elicited similar effects in the rat. Increased growth retardation, blood pooling in the head and VYS, enlarged pericardium, accumulation of necrotic matter in the amnion, and hypoplastic prosencephalon were observed in both species with all compounds. Microinjection of compounds into the amnion produced higher mortality in mouse and rat, compared to equimolar amounts added to the culture medium. CH_3OH did not prevent neural tube closure in the rat when microinjected.

CONCLUSIONS:
HCHO is the most embryotoxic CH_3OH metabolite and elicits the entire spectrum of lesions produced by CH_3OH. The VYS serves a general protective role against toxicity and inherent differences in the embryonic metabolism of CH_3OH may determine species sensitivity.

Citation:
Hansen, Jason M., Kristi M. Contreras, and Craig Harris. "Methanol, Formaldehyde, and Sodium Formate Exposure in Rat and Mouse Conceptuses: A Potential Role of the Visceral Yolk Sac in Embryotoxicity." Birth Defect Res A Birth Defects Research Part A: Clinical and Molecular Teratology 73.2 (2005)
https://pubmed.ncbi.nlm.nih.gov/15578646/

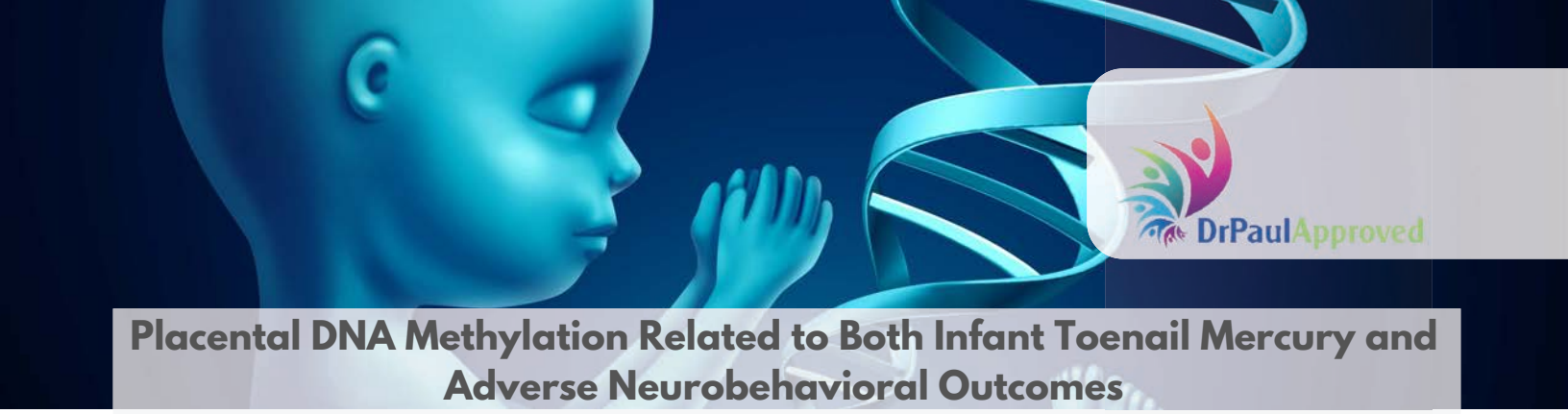
Neurobehavioural Effects of Developmental Toxicity

Abstract



Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltri-chloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.

Citation:
Bignami, G., G. Laviola, E. Alleva, R. Cagiano, C. Lacomba, and V. Cuomo. "Developmental
https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(13)70278-3/fulltext



Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes

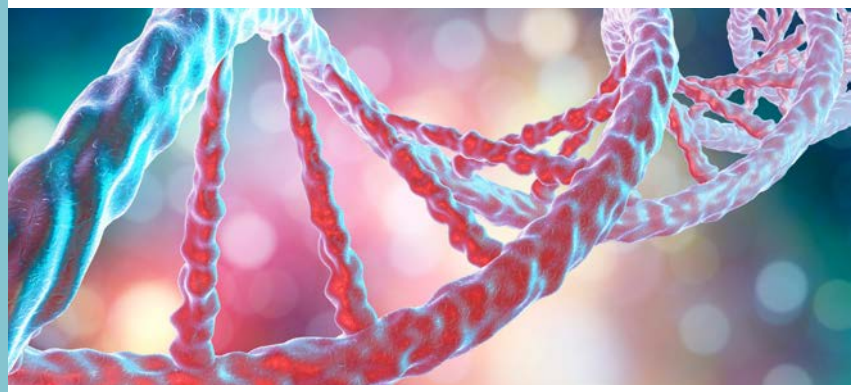
Abstract

BACKGROUND:
Prenatal mercury (Hg) exposure is associated with adverse child neurobehavioral outcomes. Because Hg can interfere with placental functioning and cross the placenta to target the fetal brain, prenatal Hg exposure can inhibit fetal growth and development directly and indirectly.

OBJECTIVES:
We examined potential associations between prenatal Hg exposure assessed through infant toenail Hg, placental DNA methylation changes, and newborn neurobehavioral outcomes.
Methods: The methylation status of > 485,000 CpG loci was interrogated in 192 placental samples using Illumina's Infinium HumanMethylation450 BeadArray. Hg concentrations were analyzed in toenail clippings from a subset of 41 infants; neurobehavior was assessed using the NICU Network Neurobehavioral Scales (NNNS) in an independent subset of 151 infants.

RESULTS:
We identified 339 loci with an average methylation difference > 0.125 between any two toenail Hg tertiles. Variation among these loci was subsequently found to be associated with a high-risk neurodevelopmental profile (omnibus p-value = 0.007) characterized by the NNNS. Ten loci had $p < 0.01$ for the association between methylation and the high-risk NNNS profile. Six of 10 loci reside in the EMID2 gene and were hypomethylated in the 16 high-risk profile infants' placentas. Methylation at these loci was moderately correlated (correlation coefficients range, −0.33 to −0.45) with EMID2 expression.

CONCLUSIONS:
EMID2 hypomethylation may represent a novel mechanism linking in utero Hg exposure and adverse infant neurobehavioral outcomes."



Citation:
Maccani, Jennifer Zeynab Joukhadar, Devin C. Koestler, Barry Lester, E. Andres. Houseman, David A. Armstrong, Karl T. Kelsey, and Carmen J. Marsit. "Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes." Environ Health Perspect Environmental Health Perspectives (2015)
https://ehp.niehs.nih.gov/doi/10.1289/ehp.1408561

Prenatal and perinatal analgesic exposure and autism: an ecological link.

Abstract

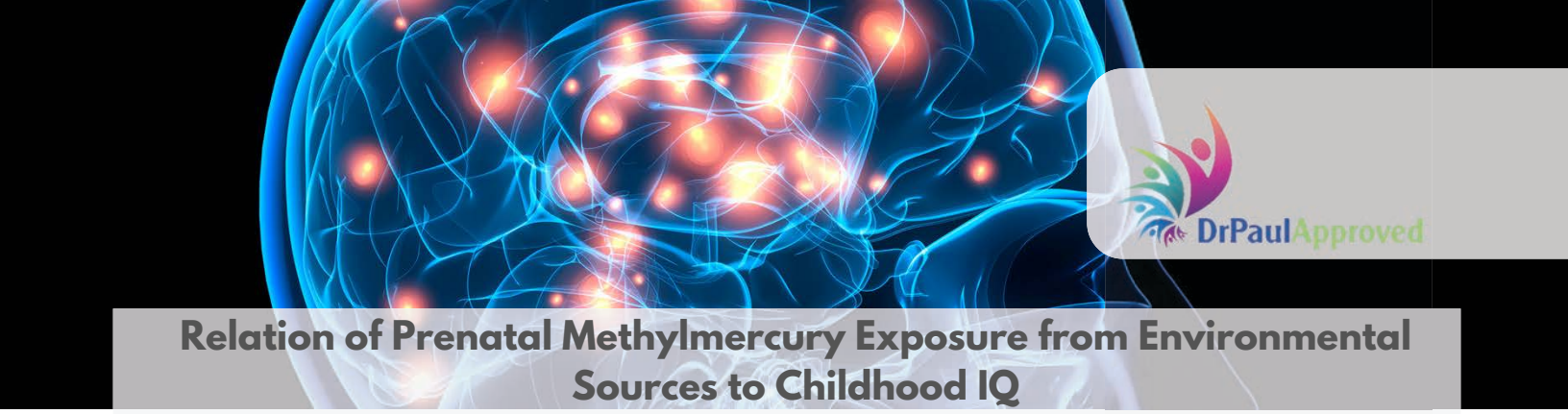
BACKGROUND:
Autism and Autism Spectrum Disorder (ASD) are complex neurodevelopmental disorders. Susceptibility is believed to be the interaction of genetic heritability and environmental factors. The synchronous rises in autism/ASD prevalence and paracetamol (acetaminophen) use, as well as biologic plausibility have led to the hypothesis that paracetamol exposure may increase
autism/ASD risk.

METHODS:
To explore the relationship of antenatal paracetamol exposure to ASD, population weighted average autism prevalence rates and paracetamol usage rates were compared. To explore the relationship of early neonatal paracetamol exposure to autism/ASD, population weighted average male autism prevalence rates for all available countries and U.S. states were compared to male circumcision rates - a procedure for which paracetamol has been widely prescribed since the mid-1990s. Prevalence studies were extracted from the U.S. Centers for Disease Control and Prevention Summary of Autism/ASD Prevalence Studies database. Maternal paracetamol usage and circumcision rates were identified by searches on Pub Med.

RESULTS:
Using all available country-level data (n = 8) for the period 1984 to 2005, prenatal use of paracetamol was correlated with autism/ASD prevalence (r = 0.80). For studies including boys born after 1995, there was a strong correlation between country-level (n = 9) autism/ASD prevalence in males and a country's circumcision rate (r = 0.98). A very similar pattern was seen among U.S. states and when comparing the 3 main racial/ethnic groups in the U.S. The country level correlation between autism/ASD prevalence in males and paracetamol was considerably weaker before 1995 when the drug became widely used during circumcision.

CONCLUSIONS:
This ecological analysis identified country-level correlations between indicators of prenatal and perinatal paracetamol exposure and autism/ASD. State level correlation was also identified for the indicator of perinatal paracetamol exposure and autism/ASD. Like all ecological analyses, these data cannot provide strong evidence of causality. However, biologic plausibility is provided by a growing body of experimental and clinical evidence linking paracetamol metabolism to pathways shown to be important in autism and related developmental abnormalities. Taken together, these ecological findings and mechanistic evidence suggest the need for formal study of the role of paracetamol in autism.

Citation:
Bauer, Ann Z., and David Kriebel. "Prenatal and Perinatal Analgesic Exposure and Autism: An Ecological Link."Environmental Health Environ Health 12.1 (2013)
https://pubmed.ncbi.nlm.nih.gov/23656698/



Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ

Abstract

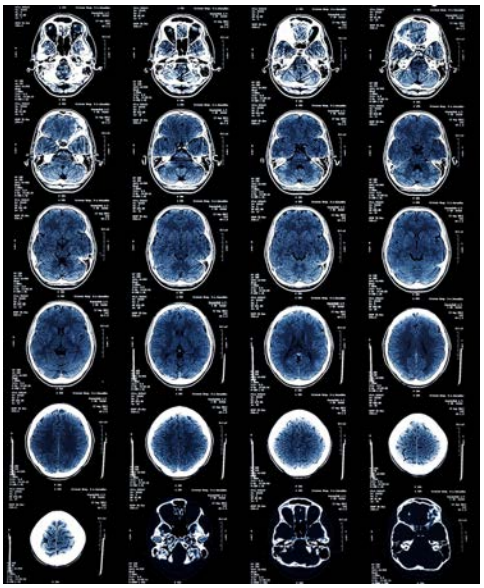
BACKGROUND:
Although prenatal methylmercury exposure has been linked to poorer intellectual function in several studies, data from two major prospective, longitudinal studies yielded contradictory results. Associations with cognitive deficits were reported in a Faroe Islands cohort, but few were found in a study in the Seychelles Islands. It has been suggested that co-exposure to another contaminant, polychlorinated biphenyls (PCBs), may be responsible for the positive findings in the former study and that co-exposure to nutrients in methylmercury-contaminated fish may have obscured and/or protected against adverse effects in the latter.

OBJECTIVES:
We aimed to determine the degree to which co-exposure to PCBs may account for the adverse effects of methylmercury and the degree to which co-exposure to docosahexaenoic acid (DHA) may obscure these effects in a sample of Inuit children in Arctic Québec.

METHODS:
IQ was estimated in 282 school-age children from whom umbilical cord blood samples had been obtained and analyzed for mercury and other environmental exposures.

RESULTS:
Prenatal mercury exposure was related to poorer estimated IQ after adjustment for potential confounding variables. The entry of DHA into the model significantly strengthened the association with mercury, supporting the hypothesis that beneficial effects from DHA intake can obscure adverse effects of mercury exposure. Children with cord mercury $\geqslant 7.5\ \mu g/L$ were four times as likely to have an IQ score < 80, the clinical cut-off for borderline intellectual disability. Co-exposure to PCBs did not alter the association of mercury with IQ.

CONCLUSIONS:
To our knowledge, this is the first study to document an association of prenatal mercury exposure with poorer performance on a school-age assessment of IQ, a measure whose relevance for occupational success in adulthood is well established. This association was seen at levels in the range within which many U.S. children of Asian-American background are exposed.

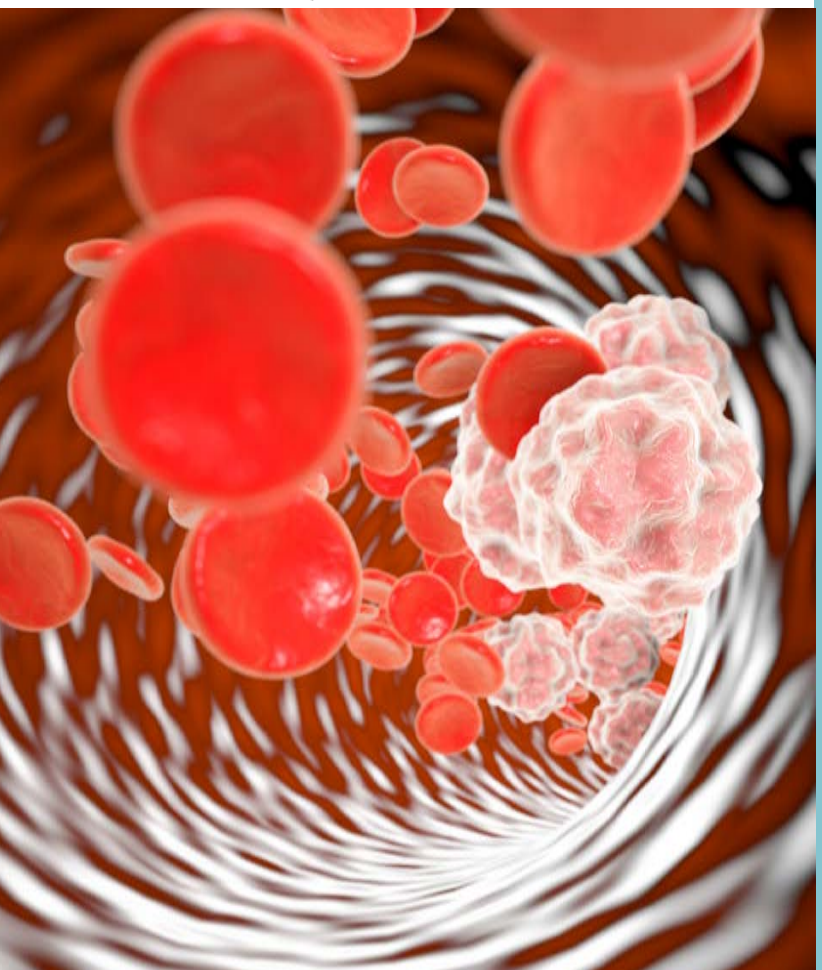


Citation:
Jacobson, Joseph L., Gina Muckle, Pierre Ayotte, Éric Dewailly, and Sandra W. Jacobson. "Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ." Environ Health Perspect Environmental Health Perspectives (2015)
https://ehp.niehs.nih.gov/doi/10.1289/ehp.1408554

Therapeutic roles of curcumin: lessons learned from clinical trials.

Abstract

Extensive research over the past half century has shown that curcumin (diferuloylmethane), a component of the golden spice turmeric (Curcuma longa), can modulate multiple cell signaling pathways. Extensive clinical trials over the past quarter century have addressed the pharmacokinetics, safety, and efficacy of this nutraceutical against numerous diseases in humans. Some promising effects have been observed in patients with various pro-inflammatory diseases including cancer, cardiovascular disease, arthritis, uveitis, ulcerative proctitis, Crohn's disease, ulcerative colitis, irritable bowel disease, tropical pancreatitis, peptic ulcer, gastric ulcer, idiopathic orbital inflammatory pseudotumor, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome, βthalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis, and chronic bacterial prostatitis. Curcumin has also shown protection against hepatic conditions, chronic arsenic exposure, and alcohol intoxication. Dose-escalating studies have indicated the safety of curcumin at doses as high as 12 g/day over 3 months. Curcumin's pleiotropic activities emanate from its ability to modulate numerous signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, NF-κB, cyclooxygenase-2, 5-LOX, STAT3, C-reactive protein, prostaglandin E(2), prostate-specific antigen, adhesion molecules, phosphorylase kinase, transforming growth factorβ, triglyceride, ET-1, creatinine, HO-1, AST, and ALT in human participants. In clinical trials, curcumin has been used either alone or in combination with other agents. Various formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets, and powder, have been examined. In this review, we discuss in detail the various human diseases in which the effect of curcumin has been investigated.



Citation:
Gupta, Subash C., Sridevi Patchva, and Bharat B. Aggarwal. "Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials." The AAPS Journal AAPS J 15.1 (2012): 195-218.
https://ehp.niehs.nih.gov/doi/10.1289/ehp.1408554

DrPaulApproved

Water fluoridation to prevent tooth decay

Abstract

Dental caries is a major public health problem in most industrialized countries, affecting 60% to 90% of school children. Community water fluoridation was initiated in the USA in 1945 and is currently practiced in about 25 countries around the world; health authorities consider it to be a key strategy for preventing dental caries. Given the continued interest in this topic from health professionals, policy makers and the public, it is important to update and maintain a systematic review that reflects contemporary evidence

Citation:
Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R, Alam R, Tugwell P, Welch V, Glenny A. "Water fluoridation for the prevention of dental caries". Cochrane Database of Systematic Reviews 2015, Issue 6.
https://www.cochrane.org/CD010856/ORAL_water-fluoridation-prevent-tooth-decay

CHAPTER 2

Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term

Abstract

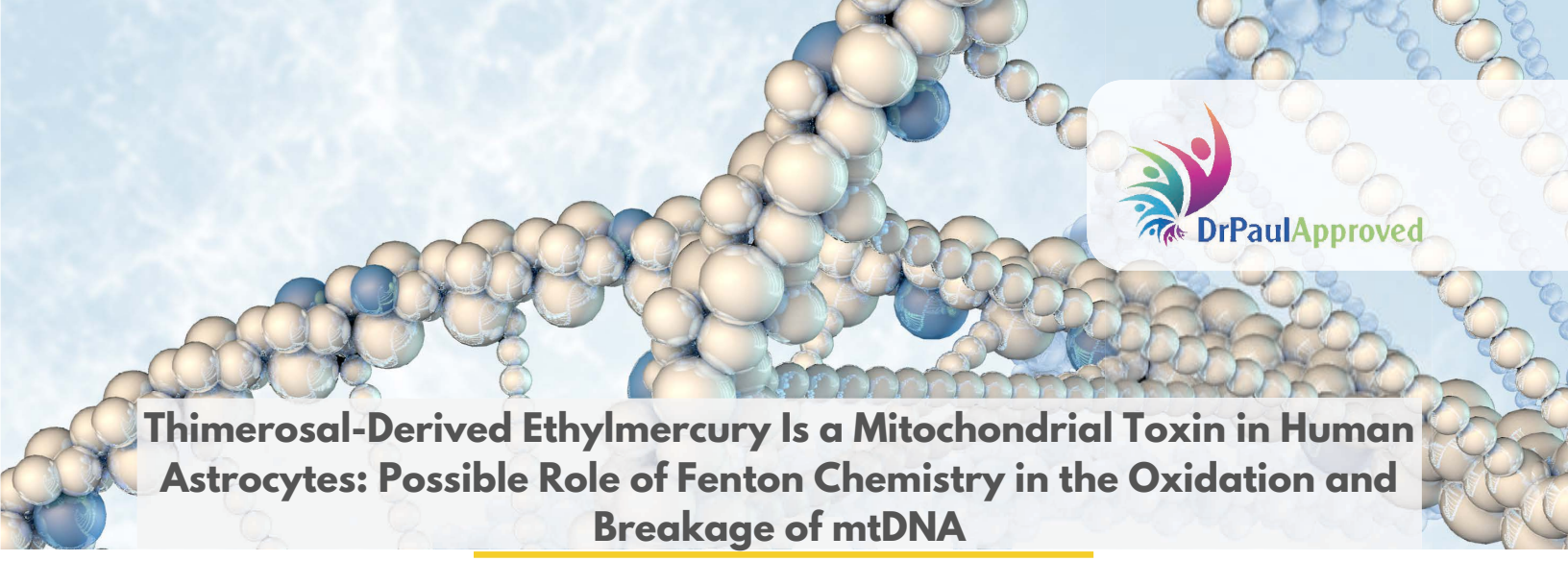
BACKGROUND:
The rate of elective primary cesarean delivery continues to rise, owing in part to the widespread perception that the procedure is of little or no risk to healthy women.

METHODS:
Using the Canadian Institute for Health Information's Discharge Abstract Database, we carried out a retrospective population-based cohort study of all women in Canada (excluding Quebec and Manitoba) who delivered from April 1991 through March 2005. Healthy women who underwent a primary cesarean delivery for breech presentation constituted a surrogate "planned cesarean group" considered to have undergone low-risk elective cesarean delivery, for comparison with an otherwise similar group of women who had planned to deliver vaginally.

RESULTS:
The planned cesarean group comprised 46,766 women v. 2,292,420 in the planned vaginal delivery group; overall rates of severe morbidity for the entire 14-year period were 27.3 and 9.0, respectively, per 1000 deliveries. The planned cesarean group had increased postpartum risks of cardiac arrest (adjusted odds ratio [OR] 5.1, 95% confidence interval [CI] 4.1-6.3), wound hematoma (OR 5.1, 95% CI 4.6-5.5), hysterectomy (OR 3.2, 95% CI 2.2-4.8), major Inpuerperal infection (OR 3.0, 95% CI 2.7- 3.4), anesthetic complications (OR 2.3, 95% CI 2.0-2.6), venous thromboembolism (OR 2.2, 95% CI 1.5-3.2) and hemorrhage requiring hysterectomy (OR 2.1, 95% CI 1.2-3.8), and stayed in hospital longer (adjusted mean difference 1.47 d, 95% CI 1.46- 1.49 d) than those in the planned vaginal delivery group, but a lower risk of hemorrhage requiring blood transfusion (OR 0.4, 95% CI 0.2-0.8). Absolute risk increases in severe maternal morbidity rates were low (e.g., for postpartum cardiac arrest, the increase with planned cesarean delivery was 1.6 per 1000 deliveries, 95% CI 1.2-2.1). The difference in the rate of in-hospital maternal death between the 2 groups was nonsignificant (p =0.87).

INTERPRETATION:
Although the absolute difference is small, the risks of severe maternal morbidity associated with planned cesarean delivery are higher than those associated with planned vaginal delivery. These risks should be considered by women contemplating an elective cesarean delivery and by their physicians.

Citation:
Liu, S., R. M. Liston, K.s. Joseph, M. Heaman, R. Sauve, and M. S. Kramer. "Maternal Mortality and Severe Morbidity Associated with Low-risk Planned Cesarean Delivery versus Planned Vaginal Delivery at Term." Canadian Medical Association Journal 176.4 (2007): 455-60.
https://pubmed.ncbi.nlm.nih.gov/17296957/

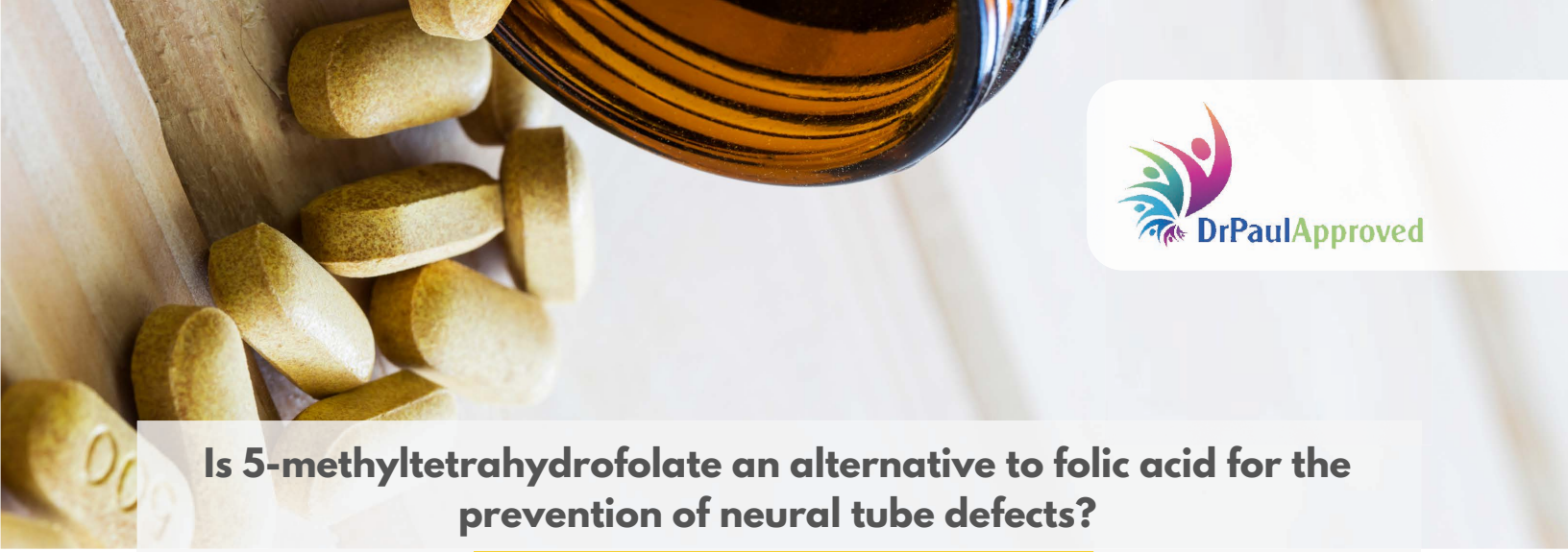


Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of mtDNA

Abstract

Thimerosal generates ethylmercury in aqueous solution and is widely used as preservative. We have investigated the toxicology of Thimerosal in normal human astrocytes, paying particular attention to mitochondrial function and the generation of specific oxidants. We find that ethylmercury not only inhibits mitochondrial respiration leading to a drop in the steady state membrane potential, but also concurrent with these phenomena increases the formation of superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical. These oxidants increase the levels of cellular aldehyde/ketones. Additionally, we find a five-fold increase in the levels of oxidant damaged mitochondrial DNA bases and increases in the levels of mtDNA nicks and blunt-ended breaks. Highly damaged mitochondria are characterized by having very low membrane potentials, increased superoxide/hydrogen peroxide production, and extensively damaged mtDNA and proteins. These mitochondria appear to have undergone a permeability transition, an observation supported by the five-fold increase in Caspase-3 activity observed after Thimerosal treatment.

Citation:
Sharpe, Martyn A., Andrew D. Livingston, and David S. Baskin. "Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of MtDNA." Journal of Toxicology 2012 (2012): 1-12.
http://www.ncbi.nlm.nih.gov/pubmed/23482308



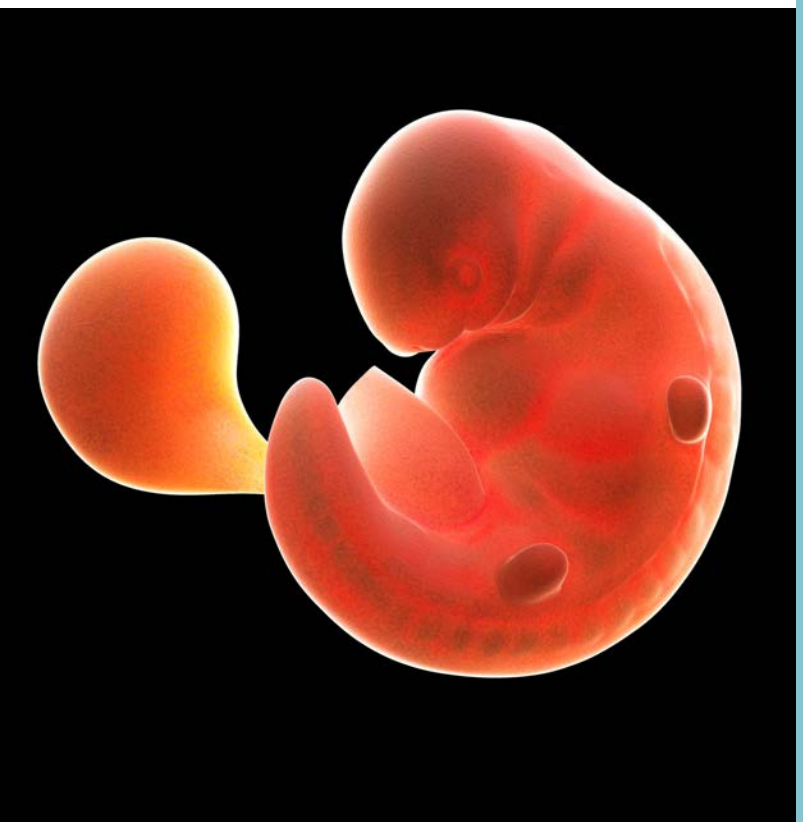
DrPaulApproved

Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects?

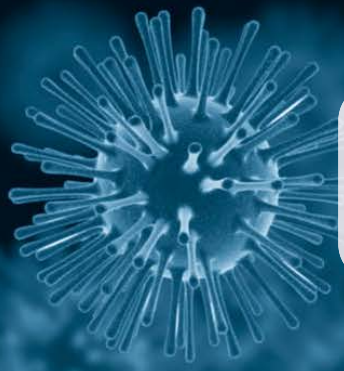
Abstract

Women have higher requirements for folate during pregnancy. An optimal folate status must be achieved before conception and in the first trimester when the neural tube closes. Low maternal folate status is causally related to neural tube defects (NTDs). Many NTDs can be prevented by increasing maternal folate intake in the preconceptional period. Dietary folate is protective, but recommending increasing folate intake is ineffective on a population level particularly during periods of high demands. This is because the recommendations are often not followed or because the bioavailability of food folate is variable.

Supplemental folate [folic acid (FA) or 5-methyltetrahydrofolate (5-methylTHF)] can effectively increase folate concentrations to the level that is considered to be protective. FA is a synthetic compound that has no biological functions unless it is reduced to dihydrofolate and tetrahydrofolate. Unmetabolized FA appears in the circulation at doses of >200 μg. Individuals show wide variations in their ability to reduce FA. Carriers of certain polymorphisms in genes related to folate metabolism or absorption can better benefit from 5-methylTHF instead of FA. 5-MethylTHF [also known as (6S)-5-methylTHF] is the predominant natural form that is readily available for transport and metabolism. In contrast to FA, 5-methylTHF has no tolerable upper intake level and does not mask vitamin B12 deficiency. Supplementation of the natural form, 5-methylTHF, is a better alternative to supplementation of FA, especially in countries not applying a fortification program. Supplemental 5-methylTHF can effectively improve folate biomarkers in young women in early pregnancy in order to prevent NTDs.



Citation:
Obeid, Rima, Wolfgang Holzgreve, and Klaus Pietrzik. "Is 5-methyltetrahydrofolate an Alternative to Folic Acid for the Prevention of Neural Tube Defects?" Journal of Perinatal Medicine 41.5 (2013). http://www.ncbi.nlm.nih.gov/pubmed/20136481



Inflammatory Responses to Trivalent Influenza Virus Vaccine Among Pregnant Women

Abstract

OBJECTIVE:
In the U.S., seasonal trivalent influenza vaccination (TIV) is currently universally recommended for all pregnant women. However, data on the maternal inflammatory response to vaccination is lacking and would better delineate the safety and clinical utility of immunization. In addition, for research purposes, vaccination has been used as a mild immune trigger to examine in vivo inflammatory responses in nonpregnant adults. The utility of such a model in pregnancy is unknown. Given the clinical and empirical justifications, the current study examined the magnitude, time course, and variance in inflammatory responses following seasonal influenza virus vaccination among pregnant women.

METHODS:
Women were assessed prior to and at one day (n=15), two days (n=10), or approximately one week (n=21) following TIV. Serum interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and macrophage migration inhibitory factor (MIF) were determined by high sensitivity immunoassay.

RESULTS:
Significant increases in CRP were seen at one and two days post-vaccination (ps <.05). A similar effect was seen for TNF-α, for which an increase at two days post-vaccination approached statistical significance (p = .06). There was considerable variability in magnitude of response; coefficients of variation for change at two days post-vaccination ranged from 122% to 728%, with the greatest variability in IL-6 responses at this timepoint.

CONCLUSIONS:
Trivalent influenza virus vaccination elicits a measurable inflammatory response among pregnant women. There is sufficient variability in response for testing associations with clinical outcomes. As adverse perinatal health outcomes including preeclampsia and preterm birth have an inflammatory component, a tendency toward greater inflammatory responding to immune triggers may predict risk of adverse outcomes, providing insight into biological mechanisms underlying risk. The inflammatory response elicited by vaccination is substantially milder and more transient than seen in infectious illness, arguing for the clinical value of vaccination. However, further research is needed to confirm that the mild inflammatory response elicited by vaccination is benign in pregnancy.

Citations:
Christian, Lisa M., Jay D. Iams, Kyle Porter, and Ronald Glaser. "Inflammatory Responses to Trivalent Influenza Virus Vaccine among Pregnant Women." Vaccine 29.48 (2011): 8982-987.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3204610/

High concentrations of folate and unmetabolized folic acid in a cohort of pregnant Canadian women and umbilical cord blood

Abstract

BACKGROUND:
Mandatory fortification, prevalent supplement use, and public health guidelines recommending periconceptional supplementation have increased folic acid intakes in North American pregnant women. However, the effects of increased folic acid intakes during pregnancy on maternal and cord blood folate concentrations have not been well established.

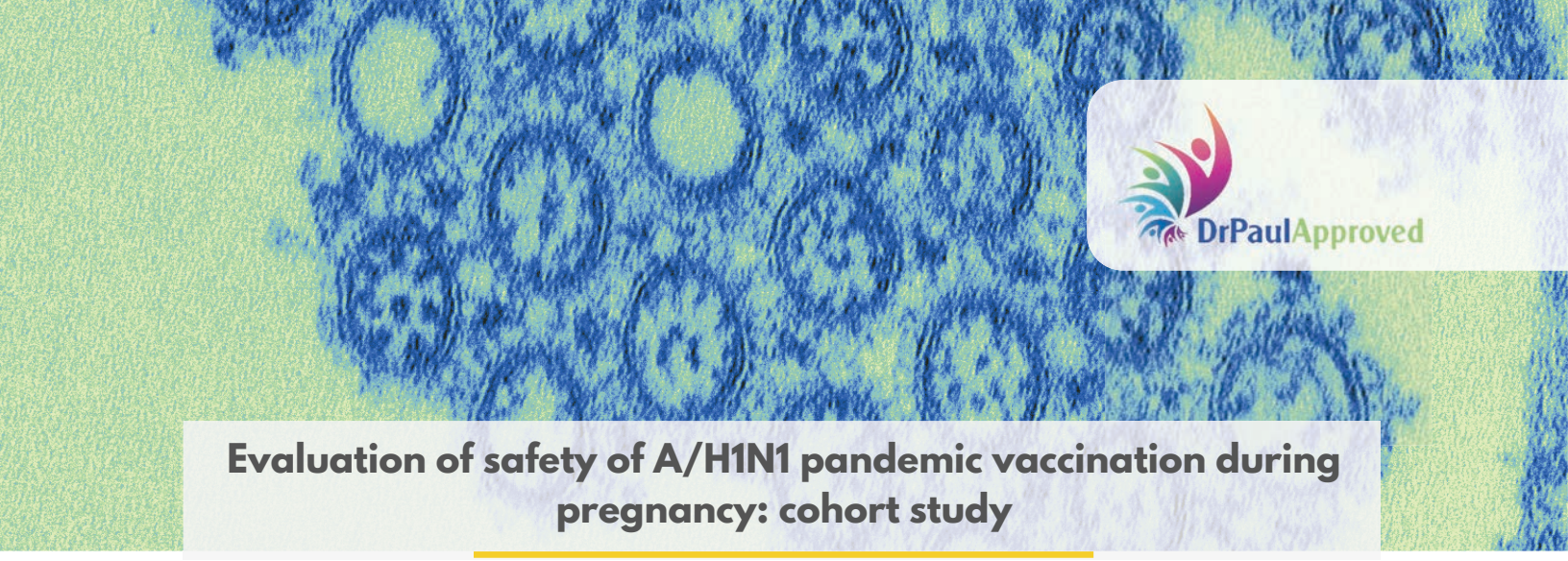
OBJECTIVES:
In this prospective study, we determined maternal and cord blood concentrations of folate and unmetabolized folic acid (UMFA) in a cohort of pregnant Canadian women and their newborns and examined the effect of maternal intakes of folate and folic acid and fetal genetic variants in folate metabolism on folate status.

DESIGN:
Folate and folic acid intakes of 368 Canadian pregnant women were assessed in early (0–16 wk) and late (23–37 wk) pregnancy. Blood concentrations of folate and UMFA were measured with the use of immunoassays and liquid chromatography–mass spectrometry, respectively, in maternal samples in early pregnancy (12–16 wk), at delivery (28–42 wk), and in cord blood. Four fetal genetic variants of the 5,10-methylenetetrahydrofolate reductase (MTHFR) and dihydrofolate reductase (DHFR) genes were assessed for their association with cord blood concentrations of folate and UMFA.

RESULTS:
Geometric mean (95% CI) maternal red blood cell (RBC) folate concentrations were 2417 nmol/L (2362, 2472 nmol/L) and 2793 nmol/L (2721, 2867 nmol/L) in early pregnancy and at delivery, respectively. The mean (95% CI) cord RBC folate concentration was 2689 nmol/L (2614, 2765 nmol/L). UMFA was detectable in >90% of maternal and cord plasma samples. Although 3 fetal MTHFRand DHFR genetic variants had no effect, the fetal MTHFR 677TT genotype was associated with significantly lower cord serum (P = 0.03) and higher cord RBC (P = 0.02) folate concentrations than those of the wild type.

CONCLUSIONS:
Notwithstanding differences in assays, maternal and cord RBC folate and plasma UMFA concentrations were higher than previously reported values. Functional ramifications of high folate and UMFA concentrations in maternal and fetal circulation warrant additional investigation because an excess folate status may affect long-term health outcomes of the offspring.

Citation:
Plumptre, L., S. P. Masih, A. Ly, S. Aufreiter, K.-J. Sohn, R. Croxford, A. Y. Lausman, H. Berger, D. L. O'connor, and Y.-I. Kim. "High Concentrations of Folate and Unmetabolized Folic Acid in a Cohort of Pregnant Canadian Women and Umbilical Cord Blood." American Journal of Clinical Nutrition 102.4 (2015): 848-57. http://ajcn.nutrition.org/content/early/2015/08/12/ajcn.115.110783



Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy: cohort study

Abstract

OBJECTIVE:
To assess the risk of maternal, fetal, and neonatal outcomes associated with the administration of an MF59 adjuvanted A/H1N1 vaccine during pregnancy.

DESIGN:
Historical cohort study.

SETTING:
Singleton pregnancies of the resident population of the Lombardy region of Italy.

PARTICIPANTS:
All deliveries between 1 October 2009 and 30 September 2010. Data on exposure to A/H1N1 pandemic vaccine, pregnancy, and birth outcomes were retrieved from regional databases. Vaccinated and non-vaccinated women were compared in a propensity score matched analysis to estimate risks of adverse outcomes.

MAIN OUTCOME MEASURES:
Main maternal outcomes included type of delivery, admission to intensive care unit, eclampsia, and gestational diabetes; fetal and neonatal outcomes included perinatal deaths, small for gestational age births, and congenital malformations.

RESULTS:
Among the 86 171 eligible pregnancies, 6246 women were vaccinated (3615 (57.9%) in the third trimester and 2557 (40.9%) in the second trimester). No difference was observed in terms of spontaneous deliveries (adjusted odds ratio 1.02, 95% confidence interval 0.96 to 1.08) or admissions to intensive care units (0.95, 0.47 to 1.88), whereas a limited increase in the prevalence of gestational diabetes (1.26, 1.04 to 1.53) and eclampsia (1.19, 1.04 to 1.39) was seen in vaccinated women. Rates of fetal and neonatal outcomes were similar in vaccinated and non-vaccinated women. A slight increase in congenital malformations, although not statistically significant, was present in the exposed cohort (1.14, 0.99 to 1.31).

CONCLUSIONS:
Our findings add relevant information about the safety of the MF59 adjuvanted A/H1N1 vaccine in pregnancy. Residual confounding may partly explain the increased risk of some maternal outcomes. Meta-analysis of published studies should be conducted to further clarify the risk of infrequent outcomes, such as specific congenital malformations.

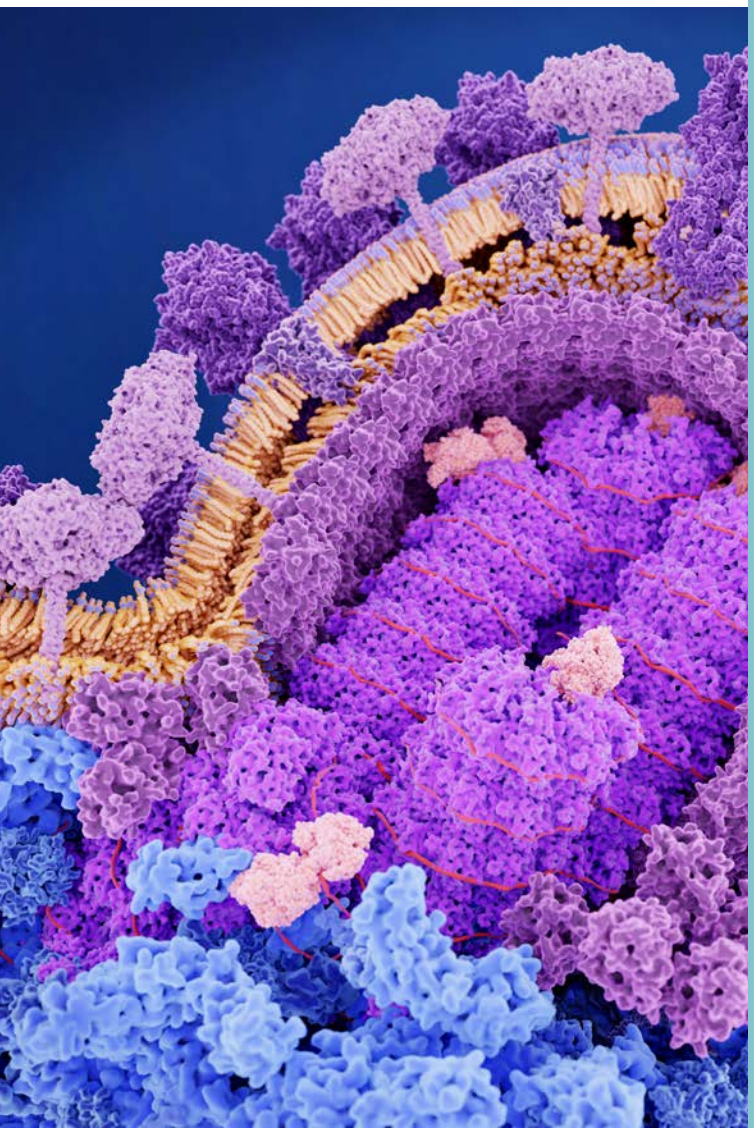
Citation:
Trotta, F., R. Da Cas, S. Spila Alegiani, M. Gramegna, M. Venegoni, C. Zocchetti, and G. Abstract Traversa. "Evaluation of Safety of A/H1N1 Pandemic Vaccination during Pregnancy: Cohort Study." BMJ 348.May29 5 (2014). https://www.bmj.com/content/348/bmj.g3361

Enhanced natural killer-cell and T-cell responses to influenza A virus during pregnancy

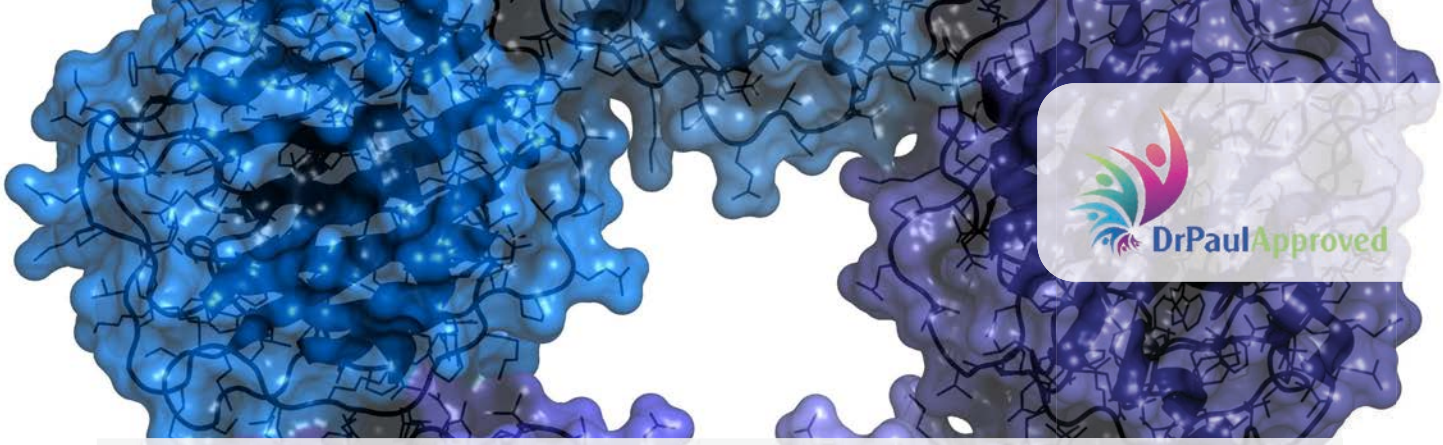
Abstract

Pregnant women experience increased morbidity and mortality after influenza infection, for reasons that are not understood. Although some data suggest that natural killer (NK)-and T-cell responses are suppressed during pregnancy, influenza-specific responses have not been previously evaluated.

Thus, we analyzed the responses of women that were pregnant (versus those that were not (Pn= 29) immediately before inactivated influenza vaccination (IIV), 7d after vaccination, and 6 wk postpartum. Expression of CD107a (a marker of cytolysis) and production of IFN-γ and macrophage inflammatory protein (MIP) 1β were assessed by flow cytometry. Pregnant women had a significantly increased percentage of NK cells producing a MIP-1β response to pH1N1 virus compared with nonpregnant women pre-IIV [median, 6.66 vs. 0.90% (= 0.0149)] and 7 d post-IIV [median, 11.23 vs. 2.81% (= 0.004)], indicating a heightened chemokine response in pregnant women that was further enhanced by the P vaccination. Pregnant women also exhibited significantly increased T-cell production of MIP-1β and polyfunctionality in NK and T cells to pH1N1 virus pre- and post-IIV. NK- and T-cell polyfunctionality was also enhanced in pregnant women in response to the H3N2 viral strain. In contrast, pregnant women had significantly reduced NK- and T-cell responses to phorbol 12-myristate 13-acetate and ionomycin. This type of stimulation led to the conclusion that NK- and T-cell responses during pregnancy are suppressed, but clearly this conclusion is not correct relative to the more biologically relevant assays described here. Robust cellular immune responses to influenza during pregnancy could drive pulmonary inflammation,explaining increased morbidity and mortality.



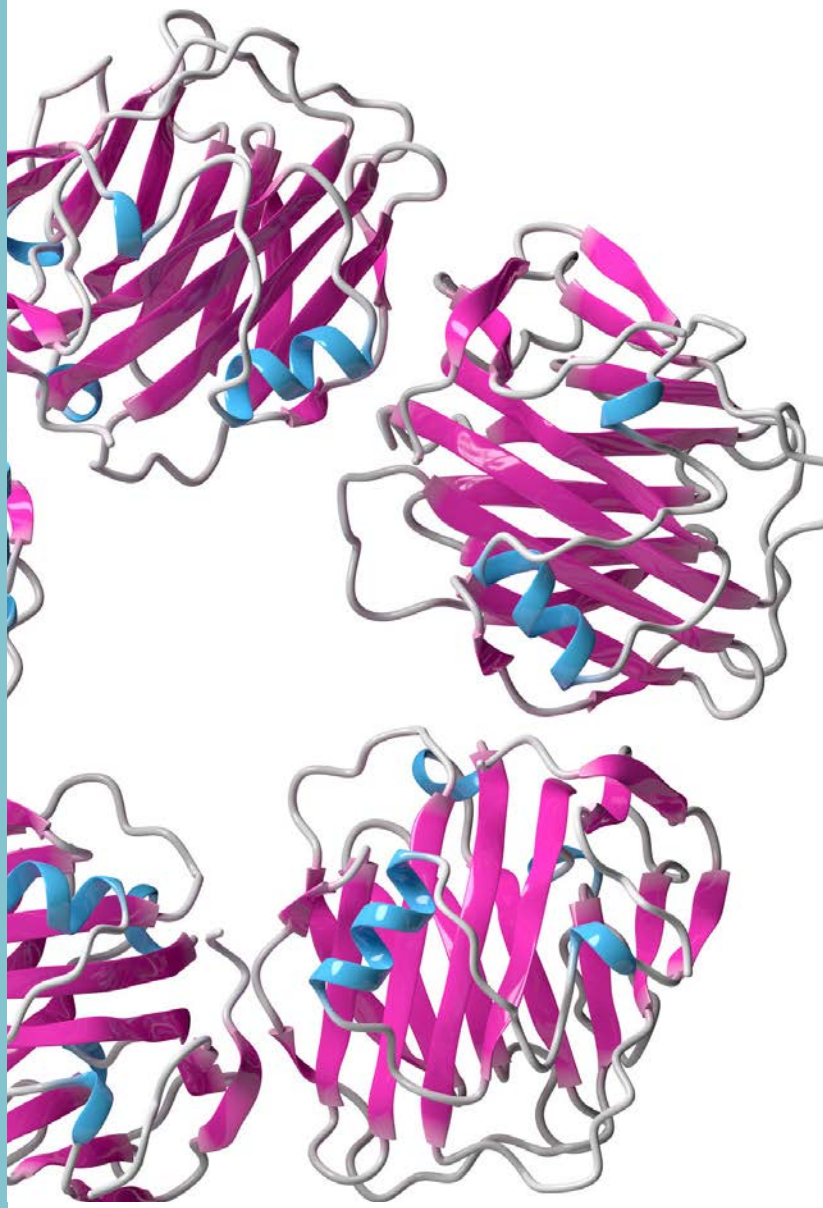
Citation:
Trotta, F., R. Da Cas, S. Spila Alegiani, M. Gramegna, M. Venegoni, C. Zocchetti, and G. Kay, Alexander W., Julia Fukuyama, Natali Aziz, Cornelia L. Dekker, Sally Mackey, Gary E. Swan, Mark M. Davis, Susan Holmes, and Catherine A. Blish. "Enhanced Natural Killer-cell and T-cell Responses to Influenza A Virus during Pregnancy." Proceedings of the National Academy of Sciences Proc Natl Acad Sci USA 111.40 (2014): 14506-4511.
https://www.pnas.org/content/111/40/14506.abstract



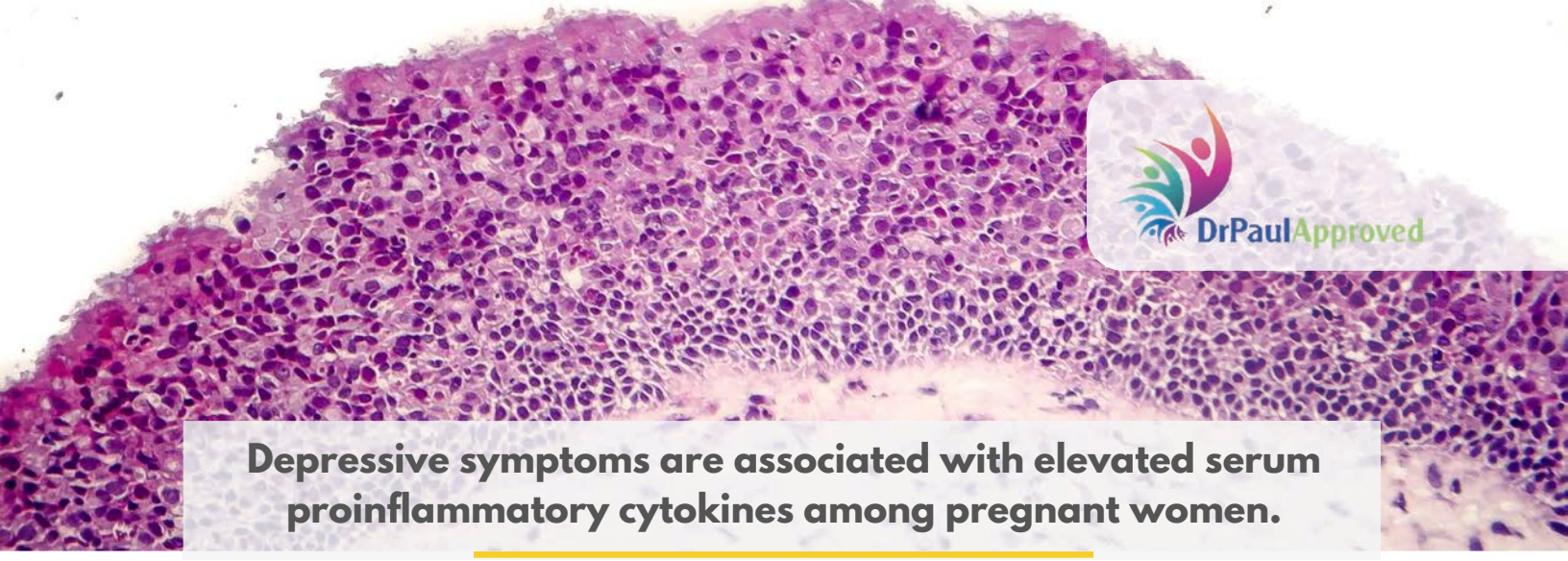
Elevated maternal C-reactive protein and autism in a national birth cohort.

Abstract

Autism is a complex neuropsychiatric syndrome with a largely unknown etiology. Inflammation during pregnancy may represent a common pathway by which infections and other insults increase risk for the disorder. Hence, we investigated the association between early gestational C-reactive protein (CRP), an established inflammatory biomarker, prospectively assayed in maternal sera, and childhood autism in a large national birth cohort with an extensive serum biobank. Other strengths of the cohort included nearly complete ascertainment of pregnancies in Finland (N=1.2 million) over the study period and national psychiatric registries consisting of virtually all treated autism cases in the population. Increasing maternal CRP levels, classified as a continuous variable, were significantly associated with autism in offspring. For maternal CRP levels in the highest quintile, compared with the lowest quintile, there was a significant, 43% elevated risk. This finding suggests that maternal inflammation may have a significant role in autism, with possible implications for identifying preventive strategies and pathogenic mechanisms in autism and other neurodevelopmental disorders.



Citation:
Brown, A. S., A. Sourander, S. Hinkka-Yli-Salomäki, I. W. Mckeague, J. Sundvall, and H-M Surcel. "Elevated Maternal C-reactive Protein and Autism in a National Birth Cohort." Molecular Psychiatry Mol Psychiatry 19.2 (2013): 259-64. http://www.ncbi.nlm.nih.gov/pubmed/23337946



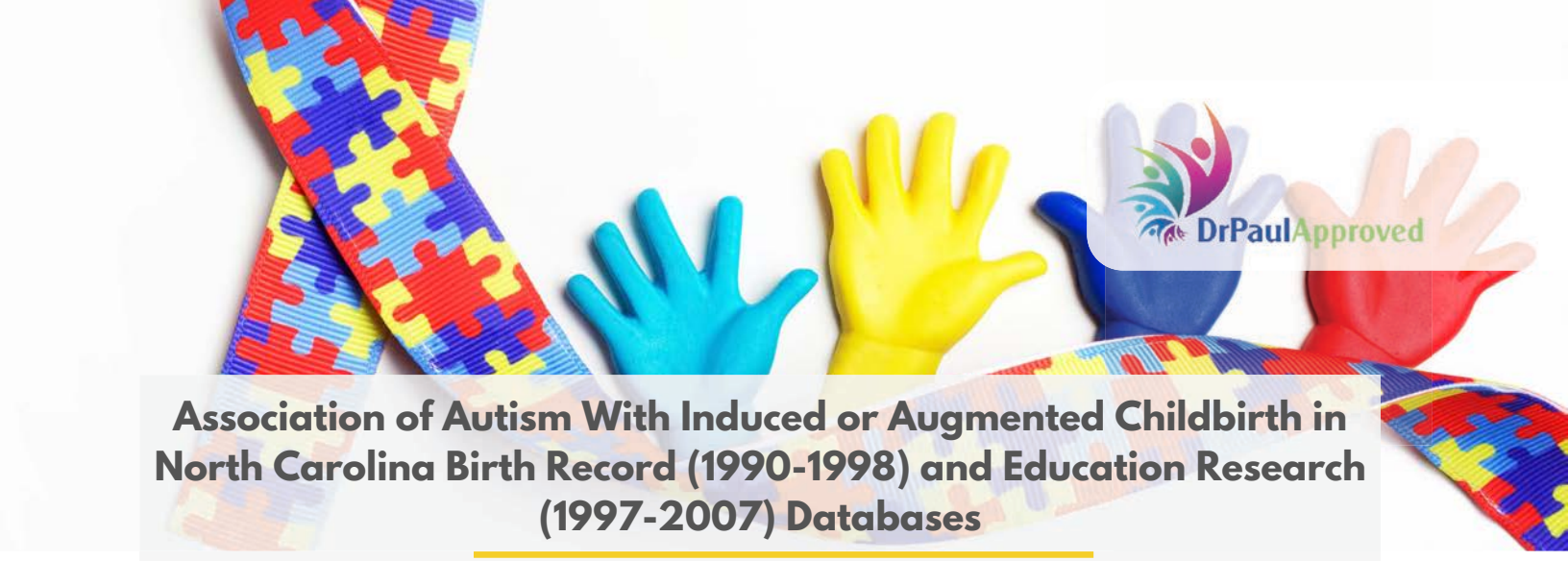
Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women.

Abstract

Psychosocial stress and depressive symptoms are associated with increased risk of negative perinatal outcomes including preterm delivery and gestational hypertension. Inflammation is a likely mechanism by which distress may promote these outcomes. It is well-established that stress and depressive symptoms are associated with elevated serum inflammatory markers in nonpregnant populations.

However, the immune system exhibits significant changes during pregnancy. Thus, the extent to which these findings extend to pregnancy is largely unknown. The current study examined associations among perceived stress, depressive symptoms, and serum inflammatory markers in a sample of 60 pregnant women. Fifty seven percent were African-American, 82% had completed high school or less education, and 63% reported an annual family income below $15,000. Participants completed the Perceived Stress Scale (PSS) and the Center for Epidemiologic Studies Depression Scale (CES-D). Serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) were determined using high sensitivity immunoassays. Regression analyses demonstrated that after controlling for pre-pregnancy Body Mass Index (BMI), higher scores on the CES-D were related to significantly higher levels of IL-6 (beta=.23, p=.05) and marginally higher TNF-alpha (beta=.24, p=.06). Perceived stress was not significantly related to serum levels of IL-6 or TNF-alpha. In sum, these results indicate that depressive symptoms are associated with higher levels of maternal serum inflammatory markers during pregnancy. These data are consistent with the contention that depressive symptoms may contribute to negative perinatal outcomes via inflammatory pathways.

Citation:
Christian LM, Franco A, Glaser R, Iams JD. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain Behav Immun. 2009 Aug;23(6):750-4. doi: 10.1016/j.bbi.2009.02.012. Epub 2009 Mar 1.
http://www.ncbi.nlm.nih.gov/pubmed/19258033



Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) Databases

Abstract

IMPORTANCE:
One in 88 children in the United States is diagnosed as having autism spectrum disorder. Significant interest centers on understanding the environmental factors that may contribute to autism risk.

OBJECTIVE:
To examine whether induced (stimulating uterine contractions prior to the onset of spontaneous labor) and/or augmented (increasing the strength, duration, or frequency of uterine contractions with spontaneous onset of labor) births are associated with increased odds of autism.

DESIGN, SETTING, AND PARTICIPANTS:
We performed an epidemiological analysis using multivariable logistic regression modeling involving the North Carolina Detailed Birth Record and Education Research databases. The study featured 625,042 live births linked with school records, including more than 5500 children with a documented exceptionality designation for autism.

EXPOSURES:
Induced or augmented births.

MAIN OUTCOMES AND MEASURES:
Autism as assessed by exceptionality designations in child educational records.

RESULTS:
Compared with children born to mothers who received neither labor induction nor augmentation, children born to mothers who were induced and augmented, induced only, or augmented only experienced increased odds of autism after controlling for potential confounders related to socioeconomic status, maternal health, pregnancy-related events and conditions, and birth year. The observed associations between labor induction/augmentation were particularly pronounced in male children.

CONCLUSIONS AND RELEVANCE:
Our work suggests that induction/augmentation during childbirth is associated with increased odds of autism diagnosis in childhood. While these results are interesting, further investigation is needed to differentiate among potential explanations of the association including underlying pregnancy conditions requiring the eventual need to induce/augment, the events of labor and delivery associated with induction/augmentation, and the specific treatments and dosing used to induce/augment labor (e.g., exogenous oxytocin and prostaglandins).

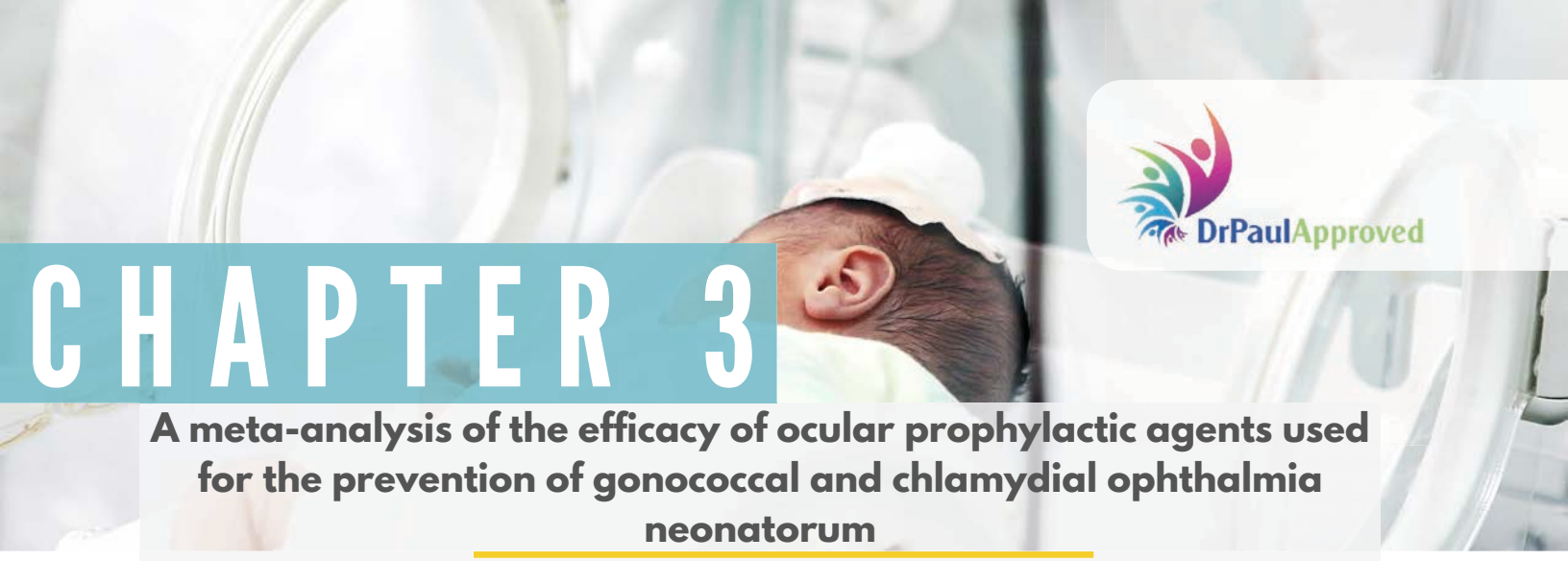
Citation:
Gregory, Simon G., Rebecca Anthopolos, Claire E. Osgood, Chad A. Grotegut, and Marie Lynn Miranda. "Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990–1998) and Education Research (1997–2007) Databases." Obstetrical & Gynecological Survey 69.1 (2014): 7-9. https://pubmed.ncbi.nlm.nih.gov/23938610/

All that palsies is not Bell's -the need to define Bell's palsy as an adverse event following immunization.

Abstract

Bell's palsy has been reported as an adverse event following immunization (AEFI). Review of the published literature reveals that several characteristics have been used to describe Bell's palsy, which differ significantly from author to author. Evidently, the definition of "Bell's palsy" remains controversial, and consensus between different medical subspecialties is urgently needed. The Brighton Collaboration has formed an international working group with representatives of neurology, otorhinolaryngology, pediatrics, electrophysiology, pharmacology, pharmaceutical and biotech industry as well as regulatory agencies to create a case definition of Bell's palsy as an AEFI.

Citation:
Rath, Barbara, Thomas Linder, David Cornblath, Michael Hudson, Rohini Fernandopulle, Katharina Hartmann, Ulrich Heininger, Hector Izurieta, Leslie Killion, Pangiotis Kokotis, James Oleske, Michael Vajdy, and Virginia Wong. ""All That Palsies Is Not Bell's [1]"— The Need to Define Bell's Palsy as an Adverse Event following Immunization." Vaccine 26.1 (2007): 1-14. https://pubmed.ncbi.nlm.nih.gov/18037542/



CHAPTER 3

A meta-analysis of the efficacy of ocular prophylactic agents used for the prevention of gonococcal and chlamydial ophthalmia neonatorum

Abstract

INTRODUCTION:
Neonatal eye prophylaxis has been routine in North America for more than a century. Contextual changes justify reexamining this practice, and prompted a systematic review of the efficacy of prophylactic agents. We searched MEDLINE (1966-2008), EMBASE (1980-2008), CINAHL (1982-2008), and the Cochrane library (the first quarter of 2008) for relevant clinical trials and hand-searched the resulting reference lists. We independently evaluated eligibility and study quality. Meta-analyses were performed using a random effects model.

RESULTS:
Each of the eight included studies had substantial methodologic weaknesses. Data to estimate the efficacy of prophylaxis in the prevention of gonococcal ophthalmia neonatorum (GON) were not available. One study found no differences in rates of chlamydial ophthalmia neonatorum (CON) when three agents were compared to no prophylaxis: silver nitrate (relative risk [RR] = 1.06; 95% confidence interval [CI], 0.55- 2.02; 2225 newborns), erythromycin (RR = 0.93; 95% CI, 0.48-1.79; 2306 newborns), and tetracycline (RR = 0.82; 95% CI, 0.42-1.63; 2299 newborns). No statistically significant differences were found between agents in the prevention of GON.

Erythromycin and povidone-iodine both decrease the risk of CON when compared to silver nitrate (RR = 0.71; 95% CI, 0.52-0.97; 4514 newborns, and RR = 0.52; 95% CI, 0.38-0.71; 2005 newborns, respectively).

DISCUSSION:
Failure rates of universal eye prophylaxis support reexamination of this policy where the prevalence of maternal infection is low.

Citation:
Darling, Elizabeth K., and Helen Mcdonald. "A Meta-analysis of the Efficacy of Ocular Prophylactic Agents Used for the Prevention of Gonococcal and Chlamydial Ophthalmia Neonatorum." Journal of Midwifery & Women's Health 55.4 (2010): 319-27.
https://pubmed.ncbi.nlm.nih.gov/20630358/

DrPaulApproved

Aluminum in pediatric parenteral nutrition products: measured versus labeled content

Abstract

OBJECTIVE:
Aluminum is a contaminant in all parenteral nutrition solutions. Manufacturers currently label these products with the maximum aluminum content at the time of expiry, but there are no published data to establish the actual measured concentration of aluminum in parenteral nutrition solution products prior to being compounded in the clinical setting. This investigation assessed quantitative aluminum content of products commonly used in the formulation of parenteral nutrition solutions. The objective of this study is to determine the best products to be used when compounding parenteral nutrition solutions (i.e., those with the least amount of aluminum contamination).

METHODS:
All products available in the United States from all manufacturers used in the production of parenteral nutrition solutions were identified and collected. Three lots were collected for each identified product. Samples were quantitatively analyzed by Mayo Laboratories. These measured concentrations were then compared to the manufacturers' labeled concentration.

RESULTS:
Large lot-to-lot and manufacturer-to-manufacturer differences were noted for all products. Measured aluminum concentrations were less than manufacturer-labeled values for all products.

CONCLUSIONS:
The actual aluminum concentrations of all the parenteral nutrition solutions were significantly less than the aluminum content based on manufacturers' labels. These findings indicate that 1) the manufacturers should label their products with actual aluminum content at the time of product release rather than at the time of expiry, 2) that there are manufacturers whose products provide significantly less aluminum contamination than others, and 3) pharmacists can select products with the lowest amounts of aluminum contamination and reduce the aluminum exposure in their patients.

Citation:
Poole, Robert L., Linda Schiff, Susan R. Hintz, Allison Wong, Nicol Mackenzie, and John A. Kerner. "Aluminum Content of Parenteral Nutrition in Neonates: Measured Versus Calculated Levels." Journal of Pediatric Gastroenterology and Nutrition 50.2 (2010): 208-11.
https://pubmed.ncbi.nlm.nih.gov/22477831/

Duration of Protection After Infant Hepatitis B Vaccination Series

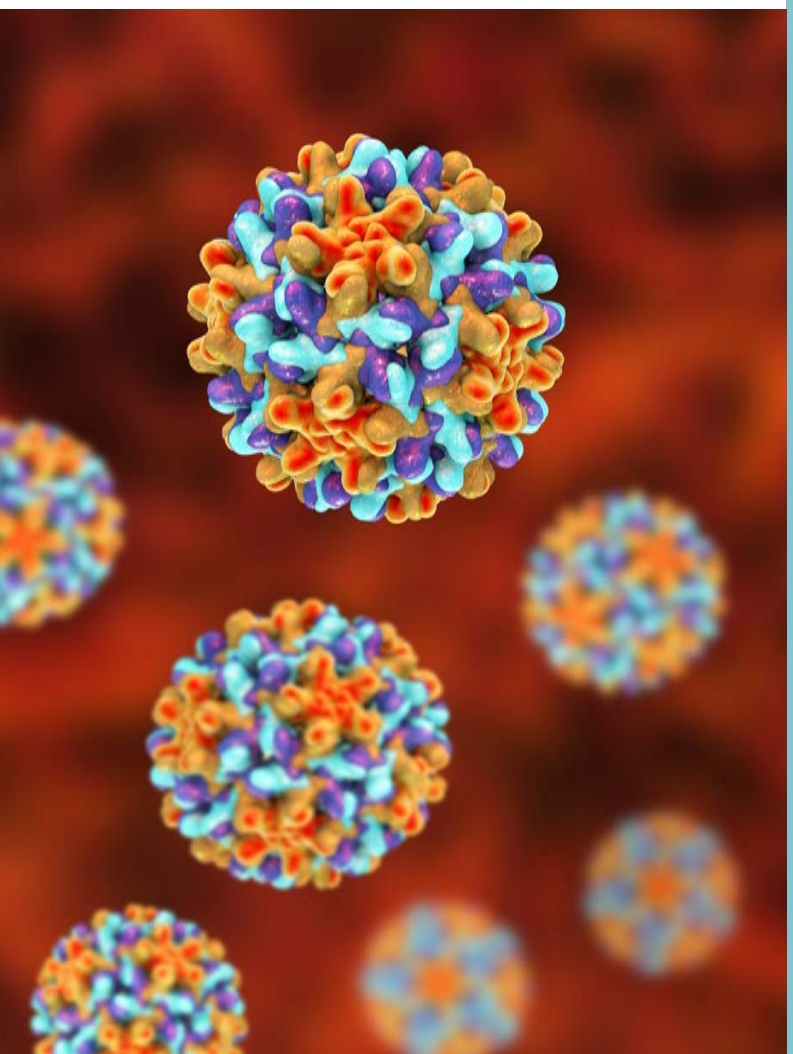
Abstract

BACKGROUND:
Little is known about duration of protection after the infant primary series of hepatitis B (HB) vaccine in settings of low HB endemicity. This study sought to determine the proportion of adolescents immunized as infants who had protective titers of antibody to hepatitis B surface antigen (anti-HBs) before and after a challenge dose of vaccine.

METHODS:
US-born 16- through 19-year-olds who received a recombinant HB vaccine 3-dose series initiated within 7 days of birth (group 1) or at ⩾4 weeks of age (group 2) and completed by 12 months of age were enrolled. Participants had serologic testing before and 2 weeks after randomization to receive a challenge dose of 10 μg or 20 μg of Engerix-B. Baseline and postchallenge levels of anti-HBs were compared by group, challenge dosage, and demographic and behavioral characteristics.

RESULTS:
At baseline, 24% had protective anti-HBs levels of ⩾10 IU/mL; 92% achieved protective levels after challenge dose. Although group 1 had a lower proportion of seroprotection at baseline, group and challenge dosage were not associated with postchallenge proportion of seroprotection. Being in group 2, higher test dosage, higher baseline geometric mean titer, and nonwhite race were associated with significantly higher geometric mean titer after challenge dose.

CONCLUSIONS:
More than 90% of study participants immunized against HB as infants exhibited a seroprotective response to a challenge dose of vaccine. Duration of protection from the primary infant HB vaccine series extended through the adolescent years in the setting of low HB endemicity.



Citation:
Amy B. Middleman, Carol J. Baker, Claudia A. Kozinetz, Saleem Kamili, Chi Nguyen, Dale J. Hu and Philip R. Spradling "Duration of Protection After Infant Hepatitis B Vaccination Series." Pediatrics 133.6 (2014).
http://pediatrics.aappublications.org/content/133/6/e1500

Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age

Abstract

IMPORTANCE:
Prevention of iron deficiency in infancy may promote neurodevelopment. Delayed umbilical cord clamping (CC) prevents iron deficiency at 4 to 6 months of age, but long-term effects after 12 months of age have not been reported.

OBJECTIVE:
To investigate the effects of delayed CC compared with early CC on neurodevelopment at 4 years of age.

DESIGN, SETTING, & PARTICIPANTS:
Follow-up of a randomized clinical trial conducted from April 16, 2008, through May 21, 2010, at a Swedish county hospital. Children who were included in the original study (n= 382) as full- term infants born after a low-risk pregnancy were invited to return for follow-up at 4 years of age. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and Movement Assessment Battery for Children (Movement ABC) scores (collected between April 18, 2012, and July 5, 2013) were assessed by a blinded psychologist. Between April 11, 2012, and August 13, 2013, parents recorded their child's development using the Ages and Stages Questionnaire, Third Edition (ASQ) and behavior using the Strengths and Difficulties Questionnaire. All data were analyzed by intention to treat.

INTERVENTIONS:
Randomization to delayed CC (≥180 seconds after delivery) or early CC (≤10 seconds after delivery).

MAIN OUTCOMES & OBJECTIVES:
The main outcome was full-scale IQ as assessed by the WPPSI-III. Secondary objectives were development as assessed by the scales from the WPPSI-III and Movement ABC, development as recorded using the ASQ, and behavior using the Strengths and Difficulties Questionnaire.

RESULTS:
We assessed 263 children (68.8%). No differences were found in WPPSI-III scores between groups. Delayed CC improved the adjusted mean differences (AMDs) in the ASQ personal-social (AMD, 2.8; 95% CI, 0.8-4.7) and fine-motor (AMD, 2.1; 95% CI, 0.2-4.0) domains and the Strengths and Difficulties Questionnaire prosocial subscale (AMD, 0.5; 95% CI, >0.0-0.9). Fewer children in the delayed-CC group had results below the cutoff in the ASQ fine-motor domain (11.0% vs 3.7%; P = .02) and the Movement ABC bicycle-trail task (12.9% vs 3.8%; P = .02). Boys who received delayed CC had significantly higher AMDs in the WPPSI-III processing-speed quotient (AMD, 4.2; 95% CI, 0.8-7.6; P = .02), Movement ABC bicycle-trail task (AMD, 0.8; 95% CI, 0.1-1.5; P = .03), and fine-motor (AMD, 4.7; 95% CI, 1.0-8.4; P = .01) and personal-social (AMD, 4.9; 95% CI, 1.6-8.3; P = .004) domains of the ASQ.

CONCLUSION & RELEVANCE:
Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country.

Citation:
Andersson, Ola, Barbro Lindquist, Magnus Lindgren, Karin Stjernqvist, Magnus Domellöf, and Lena Hellström-Westas. "Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age." JAMA Pediatrics JAMA Pediatr 169.7 (2015): 631.
http://archpedi.jamanetwork.com/article.aspx?articleid=2296145

Maternal status regulates cortical responses to the body odor of newborns

Abstract

Studies in non-human mammals have identified olfactory signals as prime mediators of mother- infant bonding and they have been linked with maternal attitudes and behavior in our own species as well. However, although the neuronal network processing infant cues has been studied for visual and auditory signals; to date, no such information exists for chemosensory signals. We contrasted the cerebral activity underlying the processing of infant odor properties in 15 women newly given birth for the first time and 15 women not given birth while smelling the body odor of unfamiliar 2 day-old newborn infants. Maternal status-dependent activity was demonstrated in the thalamus when exposed to the body odor of a newly born infant. Subsequent regions of interest analyses indicated that dopaminergic neostriatal areas are active in maternal- dependent responses. Taken together, these data suggests that body odors from 2 day-old newborns elicit activation in reward-related cerebral areas in women, regardless of their maternal status. These tentative data suggests that certain body odors might act as a catalyst for bonding mechanisms and highlights the need for future research on odor-dependent mother-infant bonding using parametric designs controlling for biological saliency and general odor perception effects.

Citation:
Lundström, Johan N., Annegret Mathe, Benoist Schaal, Johannes Frasnelli, Katharina Nitzsche, Johannes Gerber, and Thomas Hummel. "Maternal Status Regulates Cortical Responses to the Body Odor of Newborns." Frontiers in Psychology Front. Psychol. 4 (2013)
http://journal.frontiersin.org/article/10.3389/fpsyg.2013.00597/full

DrPaulApproved

Mechanisms of acetaminophen-induced cell death in primary human hepatocytes

Abstract

Acetaminophen (APAP) overdose is the most prevalent cause of drug-induced liver injury in western countries. Numerous studies have been conducted to investigate the mechanisms of injury after APAP overdose in various animal models; however, the importance of these mechanisms for humans remains unclear. Here we investigated APAP hepatotoxicity using freshly isolated primary human hepatocytes (PHH) from either donor livers or liver resections. PHH were exposed to 5mM, 10mM or 20mM APAP over a period of 48 h and multiple parameters were assessed. APAP dose-dependently induced significant hepatocyte necrosis starting from 24h, which correlated with the clinical onset of human liver injury after APAP overdose. Interestingly, cellular glutathione was depleted rapidly during the first 3h. APAP also resulted in early formation of APAP-protein adducts (measured in whole cell lysate and in mitochondria) and mitochondrial dysfunction, indicated by the loss of mitochondrial membrane potential after 12h. Furthermore, APAP time-dependently triggered c-Jun N-terminal kinase (JNK) activation in the cytosol and translocation of phospho-JNK to the mitochondria. Both co- treatment and post-treatment (3h) with the JNK inhibitor SP600125 reduced JNK activation and significantly attenuated cell death at 24h and 48h after APAP. The clinical antidote N-acetylcysteine offered almost complete protection even if administered 6h after APAP and a partial protection when given at 15h.

Citation:
Xie, Yuchao, Mitchell R. Mcgill, Kenneth Dorko, Sean C. Kumer, Timothy M. Schmitt, Jameson Forster, and Hartmut Jaeschke. "Mechanisms of Acetaminophen-induced Cell Death in Primary Human Hepatocytes." Toxicology and Applied Pharmacology 279.3 (2014): 266-74.
http://www.ncbi.nlm.nih.gov/pubmed/24905542

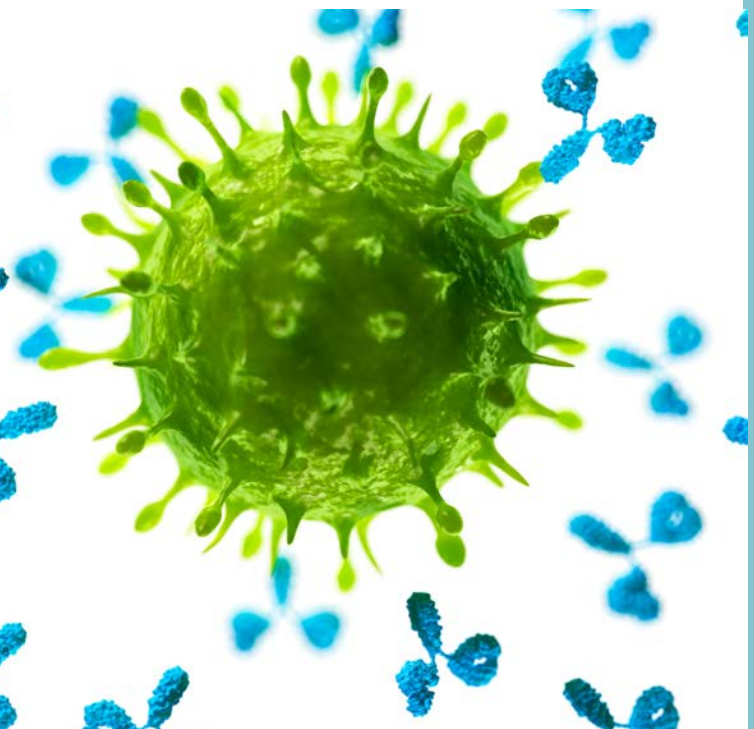
DrPaulApproved

Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations

Abstract

Immune challenges during early development, including those vaccine-induced, can lead to permanent detrimental alterations of the brain and immune function. Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of aluminum (Al) adjuvants through routine vaccinations. According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic.

Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs. When assessing adjuvant toxicity in children, several key points ought to be considered: (i) infants and children should not be viewed as "small adults" with regard to toxicological risk as their unique physiology makes them much more vulnerable to toxic insults; (ii) in adult humans Al vaccine adjuvants have been linked to a variety of serious autoimmune and inflammatory conditions (i.e., "ASIA"), yet children are regularly exposed to much higher amounts of Al from vaccines than adults; (iii) it is often assumed that peripheral immune responses do not affect brain function. However, it is now clearly established that there is a bidirectional neuro-immune cross-talk that plays crucial roles in immunoregulation as well as brain function. In turn, perturbations of the neuro-immune axis have been demonstrated in many autoimmune diseases encompassed in "ASIA" and are thought to be driven by a hyperactive immune response; and (iv) the same components of the neuro-immune axis that play key roles in brain development and immune function are heavily targeted by Al adjuvants. In summary, research evidence shows that increasing concerns about current vaccination practices may indeed be warranted. Because children may be most at risk of vaccine-induced complications, a rigorous evaluation of the vaccine-related adverse health impacts in the pediatric population is urgently needed.



Citation:
Tomljenovic, L., and C. Shaw. "Mechanisms of Aluminum Adjuvant Toxicity and Autoimmunity in Pediatric Populations." Lupus 21.2 (2012): 223-30.http://www.ncbi.nlm.nih.gov/pubmed/22235057

Ritual circumcision and risk of autism spectrum disorder in 0- to 9-year-old boys: national cohort study in Denmark

Abstract

OBJECTIVE:
Based on converging observations in animal, clinical and ecological studies, we hypothesised a possible impact of ritual circumcision on the subsequent risk of autism spectrum disorder (ASD) in young boys.

DESIGN:
National, register-based cohort study.

SETTING:
Denmark.

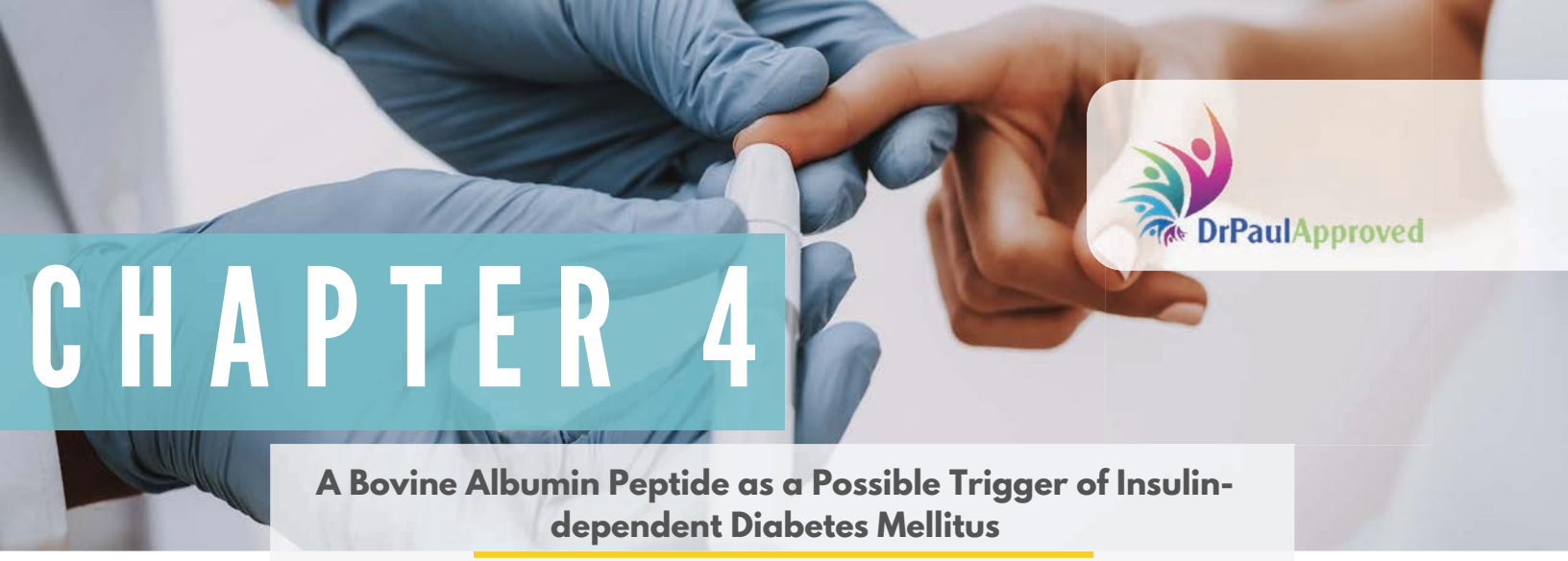
PARTICIPANTS:
A total of 342,877 boys born between 1994 and 2003 and followed in the age span 0–9 years between 1994 and 2013.

MAIN OUTCOME MEASURES:
Information about cohort members' ritual circumcisions, confounders and ASD outcomes, as well as two supplementary outcomes, hyperkinetic disorder and asthma, was obtained from national registers. Hazard ratios (HRs) with 95% confidence intervals (CIs) associated with foreskin status were obtained using Cox proportional hazards regression analyses.

RESULTS:
With a total of 4986 ASD cases, our study showed that regardless of cultural background circumcised boys were more likely than intact boys to develop ASD before age 10 years (HR = 1.46; 95% CI: 1.11–1.93). Risk was particularly high for infantile autism before age five years (HR = 2.06; 95% CI: 1.36–3.13). Circumcised boys in non-Muslim families were also more likely to develop hyperkinetic disorder (HR = 1.81; 95% CI: 1.11–2.96). Associations with asthma were consistently inconspicuous (HR = 0.96; 95% CI: 0.84–1.10).

CONCLUSIONS:
We confirmed our hypothesis that boys who undergo ritual circumcision may run a greater risk of developing ASD. This finding, and the unexpected observation of an increased risk of hyperactivity disorder among circumcised boys in non-Muslim families, need attention, particularly because data limitations most likely rendered our HR estimates conservative. Considering the widespread practice of non-therapeutic circumcision in infancy and childhood around the world, confirmatory studies should be given priority.

Citations:
Frisch, M., and J. Simonsen. "Ritual Circumcision and Risk of Autism Spectrum Disorder in 0- to 9-year-old Boys: National Cohort Study in Denmark." Journal of the Royal Society of Medicine 108.7 (2015): 266-79. http://jrs.sagepub.com/content/early/2015/01/07/0141076814565942.full



CHAPTER 4

A Bovine Albumin Peptide as a Possible Trigger of Insulin-dependent Diabetes Mellitus

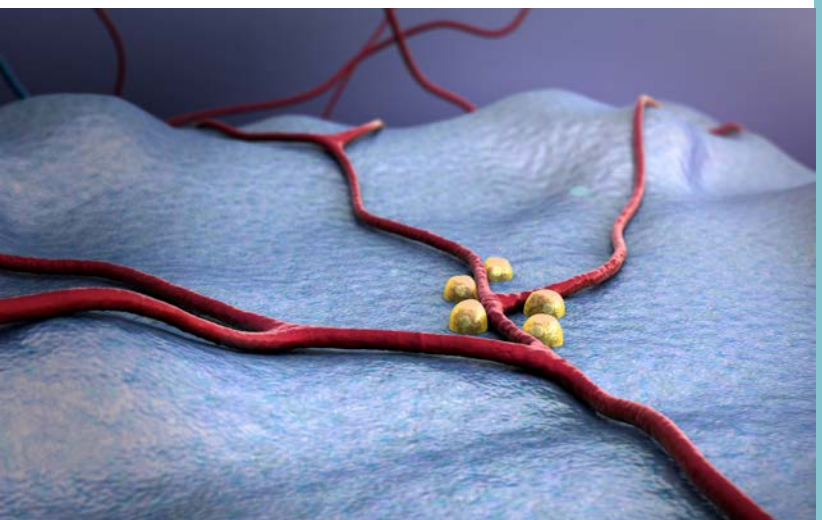
Abstract

BACKGROUND:
Cow's milk has been implicated as a possible trigger of the autoimmune response that destroys pancreatic beta cells in genetically susceptible hosts, thus causing diabetes mellitus. Studies in animals have suggested that bovine serum albumin (BSA) is the milk protein responsible, and an albumin peptide containing 17 amino acids (ABBOS) may be the reactive epitope. Antibodies to this peptide react with p69, a beta-cell surface protein that may represent the target antigen for milk-induced beta-cell--specific immunity.

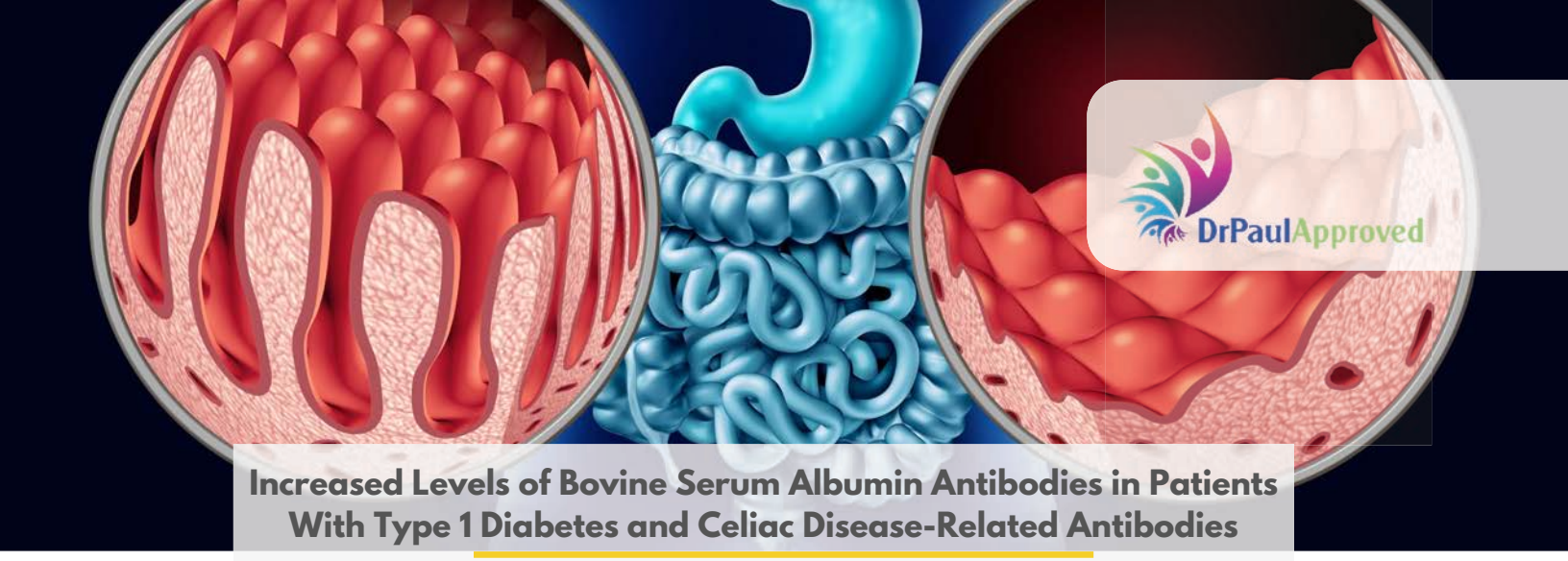
METHODS:
We used immunoassays and Western blot analysis to analyze anti-BSA antibodies in the serum of 142 children with insulin-dependent diabetes mellitus, 79 healthy children, and 300 adult blood donors. Anti-ABBOS antibodies were measured in 44 diabetic patients at the time of diagnosis, three to four months later, and one to two years later.

RESULTS:
All the diabetic patients had elevated serum concentrations of IgG anti-BSA antibodies (but not of antibodies to other milk proteins), the bulk of which were specific for ABBOS: The mean (+/- SE) concentration was 8.5 +/- 0.2 kilofluorescence units (kfU) per microliter, as compared with 1.3 +/- 0.1 kfU per microliter in the healthy children. IgA antibodies were elevated as well, but not IgM antibodies. The antibody concentrations declined after diagnosis, reaching normal levels in most patients within one to two years. The initial decline involved anti-ABBOS--specific antibodies almost exclusively. Much lower serum concentrations of anti-BSA antibodies were found in all 379 control subjects, but only 2.5 percent of them had small amounts of ABBOS- specific IgG.

CONCLUSIONS:
Patients with insulin-dependent diabetes mellitus have immunity to cow's-milk albumin, with antibodies to an albumin peptide that are capable of reacting with a beta-cell-- specific surface protein. Such antibodies could participate in the development of islet dysfunction.



Citation:
Karjalainen, J., J. M. Martin, M. Knip, J. Ilonen, B. H. Robinson, E. Savilahti, H. K. Åkerblom, H. M. Dosch, Jill Norris, and Massimo Pietropaolo. "A Bovine Albumin Peptide as a Possible Trigger of Insulin-dependent Diabetes Mellitus." Journal of Endocrinological Investigation J Endocrinol Invest 17.7 (1994): 565-72.
http://www.ncbi.nlm.nih.gov/pubmed/1377788



Increased Levels of Bovine Serum Albumin Antibodies in Patients With Type 1 Diabetes and Celiac Disease-Related Antibodies

Abstract

OBJECTIVES:
To detect the presence of antibodies against bovine serum albumin in a cohort of Spanish patients with type 1 insulin-dependent diabetes.

METHODS:
Antibodies were measured using an in-house enzyme-linked immunosorbent assay test in 80 patients with type 1 diabetes, subdivided according to the presence or absence in their serum of celiac disease-related antibodies. For comparison, 30 patients with celiac disease (nondiabetic), 13 patients with autoimmune thyroiditis, and 45 healthy volunteers were used.

RESULTS:
Thirty-one percent of patients with diabetes yielded a positive result, with a mean value of 26.1 +/- 21.8 arbitrary units (AU). If the group was split into those with celiac disease-related antibodies and those lacking them, the percentages were 53% and 25%, respectively, with a mean value of 39.6 +/- 28.4 AU and 22.4 +/- 18.3 AU (P = 0.003), respectively. Seventy-three percent of celiac patients showed bovine serum albumin antibodies with a mean level of 38.8 +/- 27.7 AU, comparable to that of patients with diabetes with celiac antibodies, but higher than the group lacking them (P = 0.001). Although 46% of patients with autoimmune thyroiditis had positive results, the level detected (22.1 +/- 8.7 AU) was significantly lower than that recorded in patients with type 1 diabetes who had celiac disease antibodies (P = 0.04) and celiac patients (P = 0.04). Healthy volunteers showed no antibodies against bovine serum albumin.

CONCLUSIONS:
These data suggest that bovine serum albumin antibodies appears in patients with a compromised epithelial permeability, and they reflect a general defect in the process of immunologic tolerance associated with a predisposition to autoimmunity, rather than immunity specific to beta cells.

Citations:
Rodríguez-Juan, Cristina, Lucía Sala-Silveira, Mercedes Pérez-Blas, Anna P. Valeri, Noemí Aguilera, Mercedes López-Santalla, Ana Fuertes, and José M. Martín-Villa. "Increased Levels of Bovine Serum Albumin Antibodies in Patients With Type 1 Diabetes and Celiac Disease-Related Antibodies." Journal of Pediatric Gastroenterology and Nutrition 37.2 (2003): 132-35. http://www.ncbi.nlm.nih.gov/pubmed/12883297

Parental Well-being Surrounding First Birth as a Determinant of Further Parity Progression

Abstract

A major component driving cross-country fertility differences in the developed world is differences in the probability of having additional children among those who have one. Why do people stop at having only one child? We hypothesize that the experience of the transition to parenthood is an important determinant of further fertility. Analyzing longitudinal data from Germany, we find that the experience during the transition to parenthood, as measured by changes in subjective well-being, predicts further parity progression. A drop in well-being surrounding first birth predicts a decreased likelihood of having another child. The association is particularly strong for older parents and those with higher education: these characteristics may be related to the ability or willingness to revise fertility plans based on prior experiences. Parents' experience with the first birth is an important and understudied factor in determining completed family size, and policy-makers concerned about low fertility should pay attention to factors that influence the well-being of new parents.

Citation:
Margolis, Rachel, and Mikko Myrskylä. "Parental Well-being Surrounding First Birth as a Determinant of Further Parity Progression." Demography 52.4 (2015): 1147-166.
http://link.springer.com/article/10.1007/s13524-015-0413-2

Randomized, controlled trial of division of tongue-tie in infants with feeding problems.

Abstract

OBJECTIVE:
To determine whether, in infants with a tongue-tie and a feeding problem, the current medical treatment (referral to a lactation consultant) or immediate division works best and enables the infants to feed normally.

METHODS:
Between March and July 2002, all the babies in the district of Southampton with tongue-ties were followed in order to see if they had any feeding problems. If they developed problems, the mothers gave written consent and were enrolled in an ethics committee approved, randomized, controlled trial, comparing 48 h of intensive lactation consultant support (control) with immediate division.

RESULTS:
A total of 201 babies had tongue-tie, of whom 88 had breast-feeding or bottle-feeding problems. Thirty-one were not enrolled, so 57 were randomized. Of the 29 controls, one improved (3%) and breast-fed for 8 months, but 28 did not. At 48 h, these 28 were offered division, which all accepted, and 27 improved (96%) and fed normally. Of the 28 babies who had immediate division, 27 improved and fed normally but one remained on a nipple shield (P < 0.001). Twenty-four mothers breast-fed for 4 months (24/40, 60%). Overall, division of the tongue-tie babies resulted in improved feeding in 54/57 (95%) babies.

CONCLUSIONS:
This randomized, controlled trial has clearly shown that tongue-ties can affect feeding and that division is safe, successful and improved feeding for mother and baby significantly better than the intensive skilled support of a lactation consultant.

Citation:
Hogan, Monica, Carolyn Westcott, and Mervyn Griffiths. "Randomized, Controlled Trial of Division of Tongue-tie in Infants with Feeding Problems." Journal of Paediatrics and Child Health J Paediatr Child Health 41.5-6 (2005): 246-50. http://www.ncbi.nlm.nih.gov/pubmed/15953322

Treatment of Ankyloglossia and Breastfeeding Outcomes: A Systematic Review Abstract

Abstract

OBJECTIVE:
Ankyloglossia is a congenital condition characterized by an abnormally short, thickened, or tight lingual frenulum that restricts tongue mobility. The objective of this study was to systematically review literature on surgical and nonsurgical treatments for infants with ankyloglossia.

METHODS:
Medline, PsycINFO, Cumulative Index of Nursing and Allied Health Literature, and Embase were searched up to August 2014. Two reviewers independently assessed studies against predetermined inclusion/exclusion criteria. Two reviewers independently extracted data regarding participant and intervention characteristics and outcomes and assigned quality and strength-of-evidence ratings.

RESULTS:
Twenty-nine studies reported breastfeeding effectiveness outcomes (5 randomized controlled trials [RCTs], 1 retrospective cohort, and 23 case series). Four RCTs reported improvements in breastfeeding efficacy by using either maternally reported or observer ratings, whereas 2 RCTs found no improvement with observer ratings. Although mothers consistently reported improved effectiveness after frenotomy, outcome measures were heterogeneous and short-term. Based on current literature, the strength of the evidence (confidence in the estimate of effect) for this issue is low. We included comparative studies published in English. The evidence base is limited, consisting of small studies, short-term outcomes, and little information to characterize participants adequately. No studies addressed nonsurgical interventions, longer-term breastfeeding or growth outcomes, or surgical intervention compared with other approaches to improve breastfeeding, such as lactation consultation

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CONCLUSIONS:
A small body of evidence suggests that frenotomy may be associated with mother-reported improvements in breastfeeding, and potentially in nipple pain, but with small, short-term studies with inconsistent methodology, strength of the evidence is low to insufficient.

Citation:
Francis, D. O., S. Krishnaswami, and M. Mcpheeters. "Treatment of Ankyloglossia and Breastfeeding Outcomes: A Systematic Review." Pediatrics 135.6 (2015)
http://pediatrics.aappublications.org/content/early/2015/04/28/peds.2015-0658

DrPaulApproved

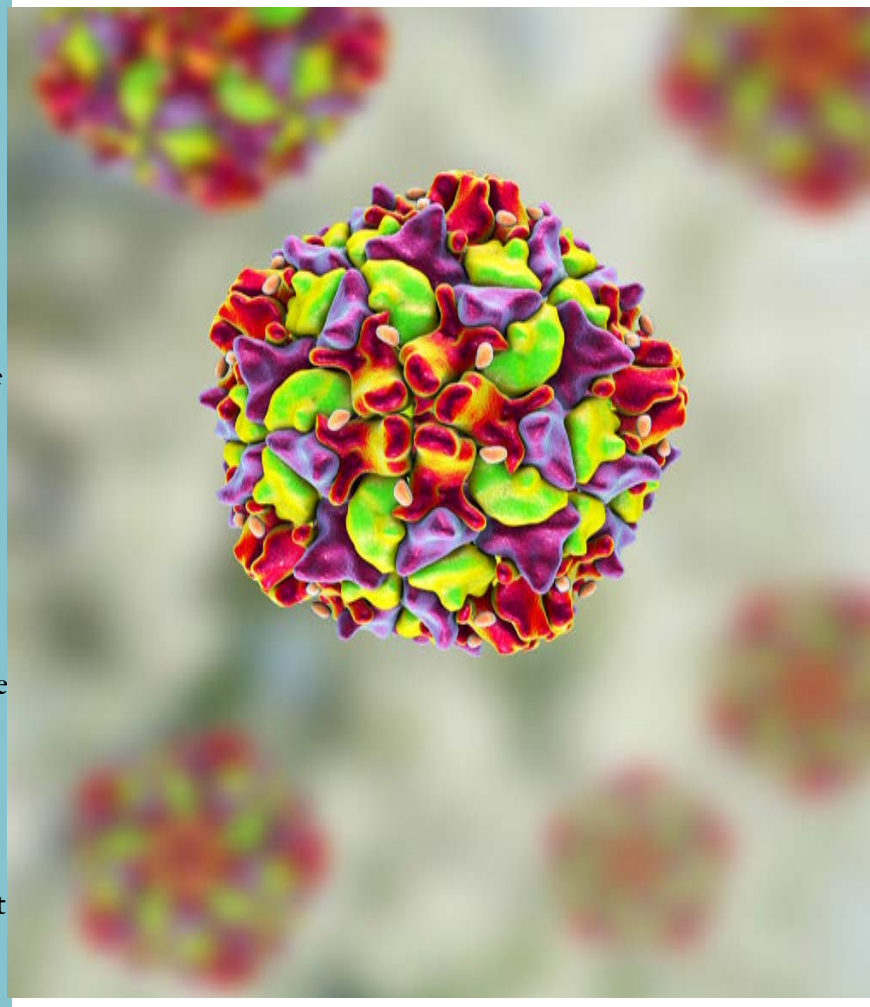
CHAPTER 5

"A calculated risk": the Salk polio vaccine field trials of 1954

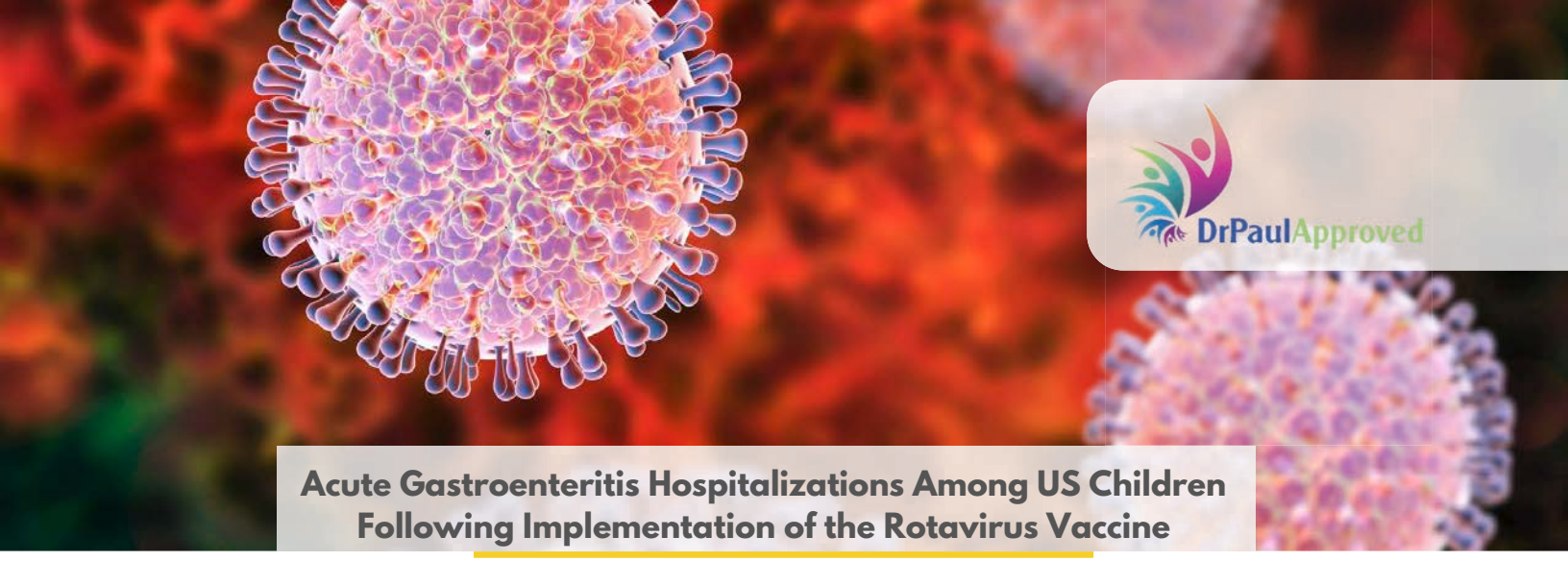
Abstract

The polio vaccine field trials of 1954, sponsored by the National Foundation for Infantile Paralysis (March of Dimes), are among the largest and most publicised clinical trials ever undertaken. Across the United States, 623 972 schoolchildren were injected with vaccine or placebo, and more than a million others participated as "observed" controls. The results, announced in 1955, showed good statistical evidence that Jonas Salk's killed virus preparation was 80-90% effective in preventing paralytic poliomyelitis. The statistical design used in this great experiment was singular, prompting criticism at the time and since. Eighty four test areas in 11 states used the textbook model: in a randomised, blinded design all participating children in the first three grades of school (ages 6-9) received injections of either vaccine or placebo and were observed for evidence of the disease. But 127 test areas in 33 states used an "observed control" design: participating children in the second grade (ages 7-8) received injections of vaccine; no placebo was given, and children in all three grades were then observed for the duration of the polio "season." The use of the dual protocol illustrates both the power and the limitations of the randomised clinical trial to legitimate therapeutic claims. The placebo controlled trials were necessary to define the Salk vaccine—introduced by a lay organisation that has taken an activist position against the counsel of its virological advisers—as the product of scientific medicine.

The observed control trials were essential to maintaining public support for the vaccine as the product of lay faith and investment in science. Here I examine the process by which the trial design was negotiated and the roles of the several actors.

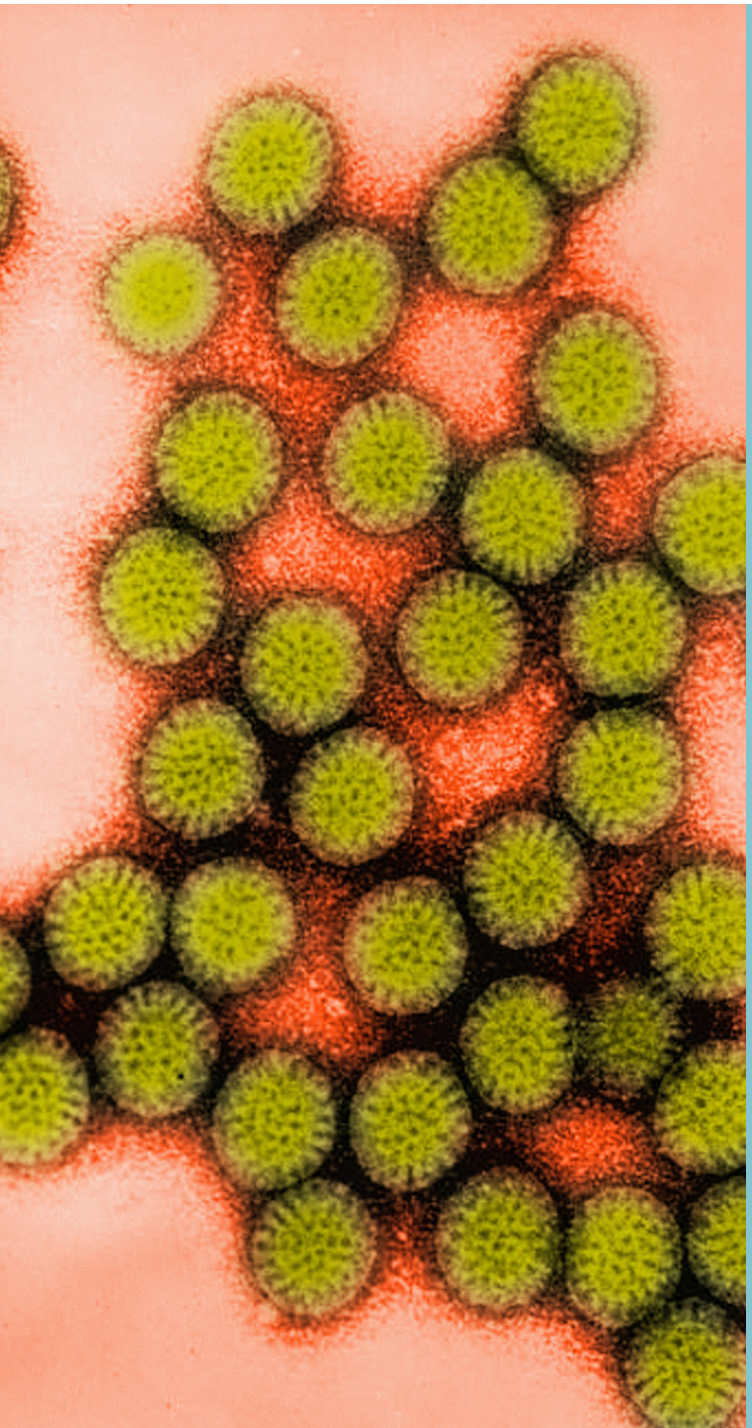


Citation:
Meldrum, M. ""A Calculated Risk": The Salk Polio Vaccine Field Trials of 1954."
Bmj 317.7167 (1998): 1233-236.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1114166/



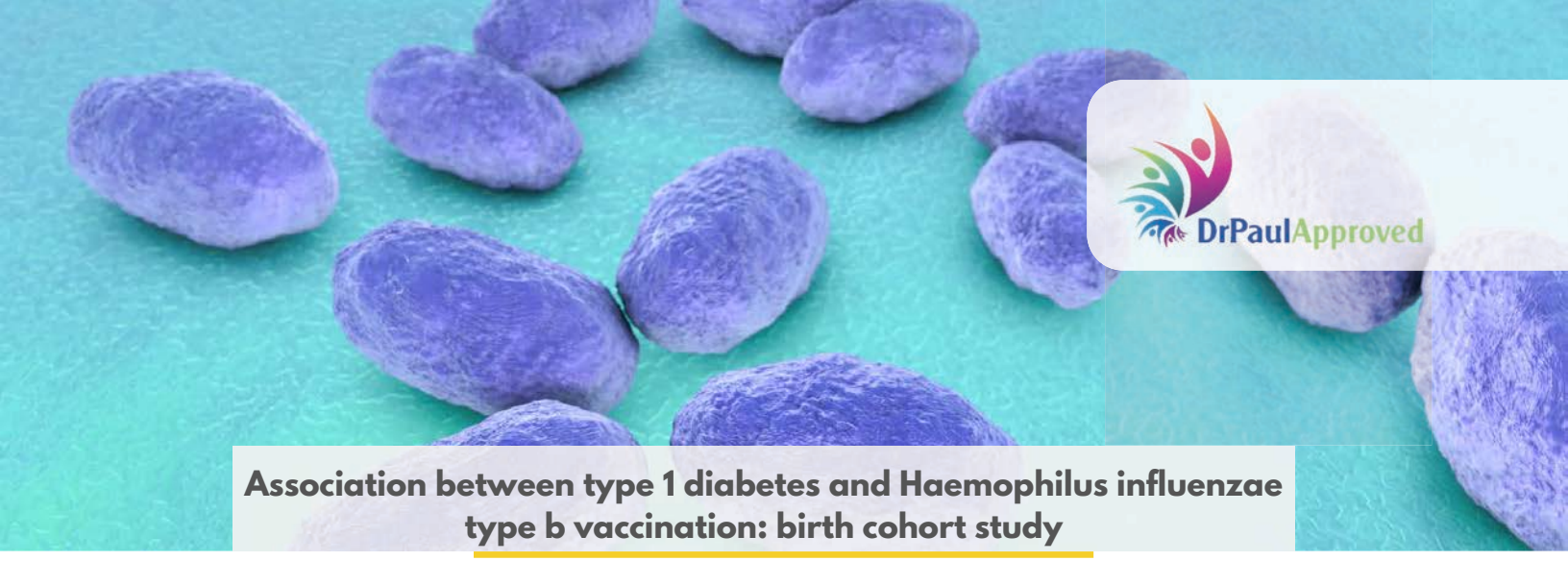
Acute Gastroenteritis Hospitalizations Among US Children Following Implementation of the Rotavirus Vaccine

Abstract



Routine rotavirus vaccination of US children was implemented in 2006, with 2 or 3 doses recommended before the age of 8 months.1 Previous studies have demonstrated the association of rotavirus vaccine introduction with reductions in health care use during the early postintroduction period or with limited insurance databases.2-4 Because laboratory testing and coding for rotavirus are not routinely performed for patients with diarrhea, we examined both all-cause acute gastroenteritis and rotavirus-coded hospitalizations among children younger than 5 years from 2000 through 2012.

Citation:
Leshem, Eyal, Jacqueline E. Tate, Claudia A. Steiner, Aaron T. Curns, Ben A. Lopman, and Umesh D. Parashar. "Acute Gastroenteritis Hospitalizations Among US Children Following Implementation of the Rotavirus Vaccine." Jama 313.22 (2015): 2282.
https://jamanetwork.com/journals/jama/fullarticle/2319155



Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study

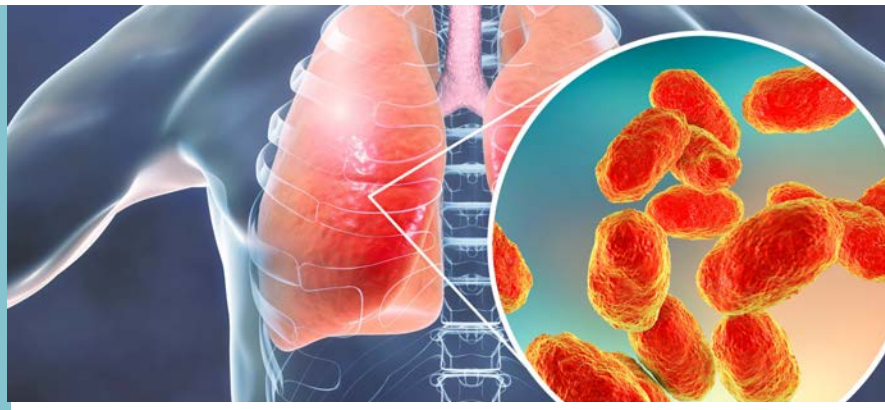
Abstract

OBJECTIVES:
To determine the effect of Haemophilus influenzae type b vaccination and its timing on the risk of type 1 diabetes in Finnish children.

DESIGN:
Cumulative incidence and relative risk of type 1 diabetes was compared among three birth cohorts of Finnish children: those born during the 24 months before the H influenzae type b vaccination trial, those in the trial cohort who were vaccinated at 3 months of age and later with a booster vaccine, and those in the trial cohort who were vaccinated at 24 months of age only. The probability of type 1 diabetes was estimated using regression analysis assuming that there were no losses to 10 year follow up and no competing risks.

SETTING:
Finland (total population 5 million and annual birth rate 1.3%).

SUBJECTS:
128 936 children born from 1 October 1983 to 1 September 1985, and 116 352 children born from 1 October 1985 to 31 August 1987.



MAIN OUTCOME MEASURES:
Probability of type 1 diabetes among children vaccinated withH influenzae type b and non- vaccinated children.

RESULTS:
No statistically significant difference was found at any time during the 10 year follow up in the risk of type 1 diabetes between the children born before the vaccination period and those vaccinated at the age of 24 months only (relative risk 1.01). The difference in the risk between the cohort vaccinated first at the age of 3 months and the cohort vaccinated at the age of 24 months only was not statistically significant either (1.06).

CONCLUSION:
It is unlikely that H influenzae type b vaccination or its timing cause type 1 diabetes in children.

Citation:
Karvonen, M., Z. Cepaitis, and J. Tuomilehto. "Association between Type 1 diabetes and Haemophilus Influenzae Type B Vaccination: Birth Cohort Study." Bmj 318.7192 (1999): 1169-172.
http://www.bmj.com/content/318/7192/1169

Childhood Intussusception: A Literature Review

Abstract

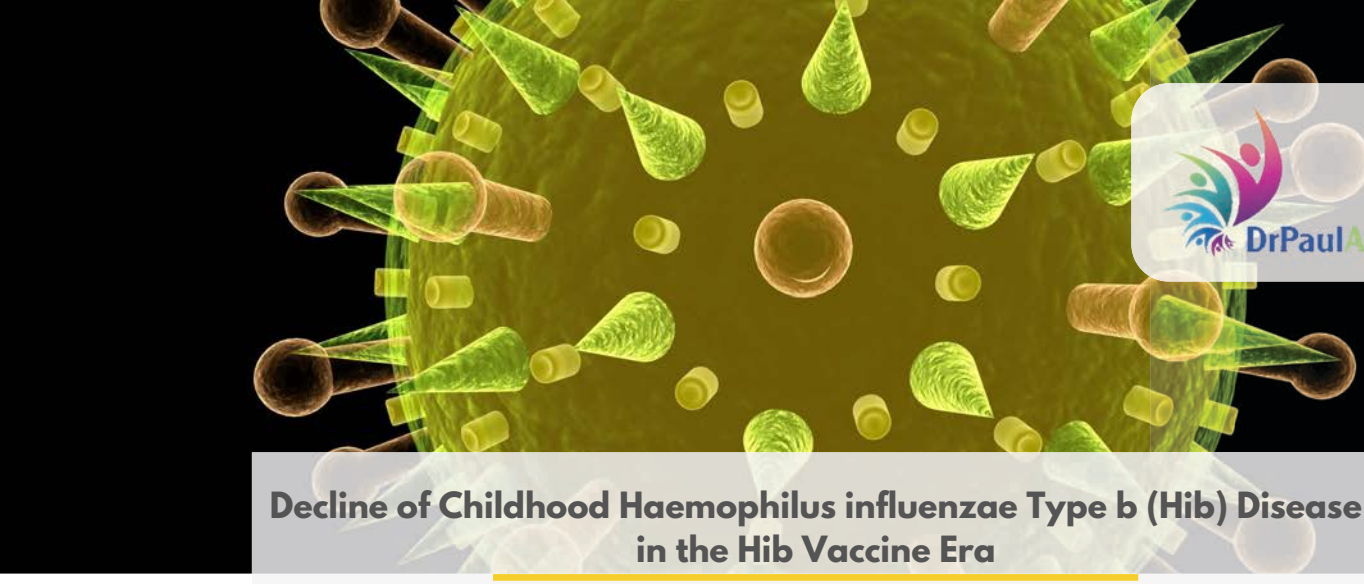
BACKGROUND:
Postlicensure data has identified a causal link between rotavirus vaccines and intussusception in some settings. As rotavirus vaccines are introduced globally, monitoring intussusception will be crucial for ensuring safety of the vaccine programs.

METHODS:
To obtain updated information on background rates and clinical management of intussusception, we reviewed studies of intussusception in children <18 years of age published since 2002. We assessed the incidence of intussusception by month of life among children <1 year of age, seasonality, method of diagnosis, treatment, and case-fatality.

FINDINGS:
We identified 82 studies from North America, Asia, Europe, Oceania, Africa, Eastern Mediterranean, and Central & South America that reported a total of 44,454 intussusception events. The mean incidence of intussusception was 74 per 100,000 (range: 9–328) among children <1 year of age, with peak incidence among infants 5–7 months of age. No seasonal patterns were observed. A radiographic modality was used to diagnose intussusception in over 95% of the cases in all regions except Africa where clinical findings or surgery were used in 65% of the cases. Surgical rates were substantially higher in Africa (77%) and Central and South America (86%) compared to other regions (13–29%). Case-fatality also was higher in Africa (9%) compared to other regions (<1%). The primary limitation of this review relates to the heterogeneity in intussusception surveillance across different regions.

CONCLUSION:
This review of the intussusception literature from the past decade provides pertinent information that should facilitate implementation of intussusception surveillance for monitoring the postlicensure safety of rotavirus vaccines.

Citation:
Jiang, James, Baoming Jiang, Umesh Parashar, Trang Nguyen, Julie Bines, and Manish M. Patel. "Childhood Intussusception: A Literature Review." PLoS ONE 8.7 (2013)
http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0068482



Decline of Childhood Haemophilus influenzae Type b (Hib) Disease in the Hib Vaccine Era

Abstract

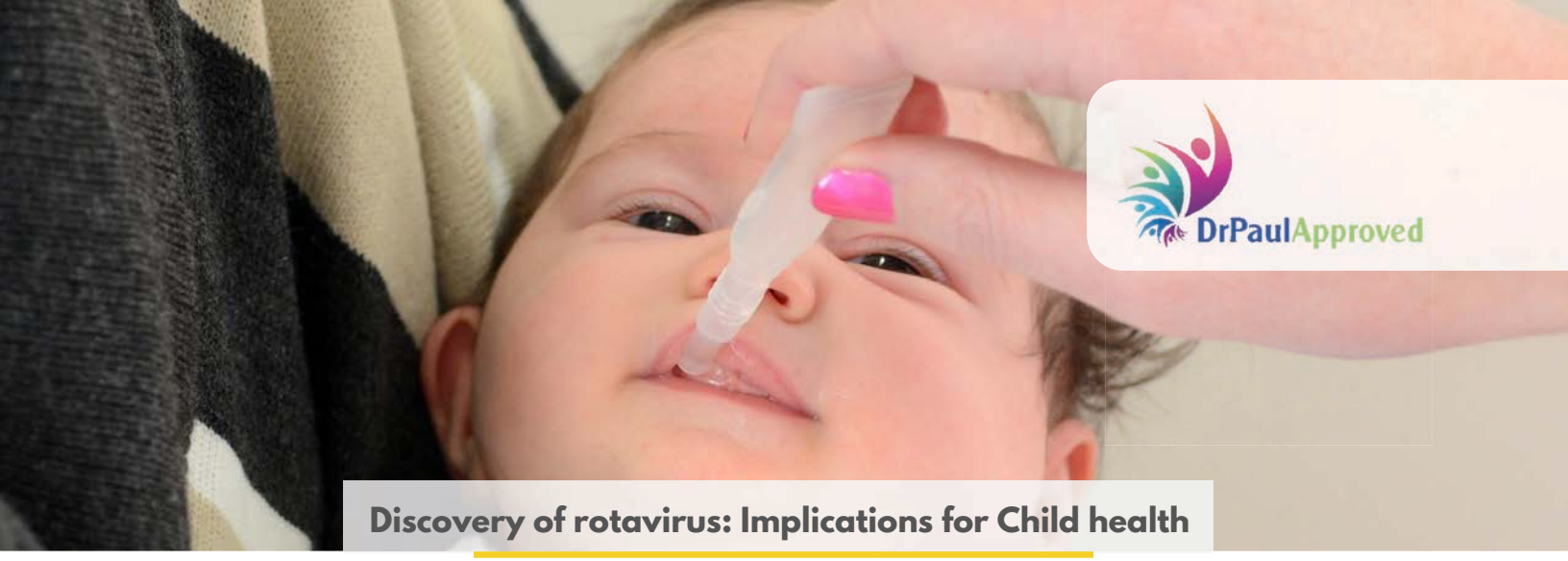
OBJECTIVE:
Effective Haemophilus influenza type b (Hib) conjugate vaccines were first licensed for use in US children at least 18 months old in December 1987 and for infants at least 2 months old in October 1990. We evaluated trends in Hib disease associated with licensure of Hib conjugate vaccines.

DESIGN:
Data from two sources, an intensive laboratory-based active surveillance system and the National Bacterial Meningitis Reporting System (NBMRS), were used separately to evaluate disease incidence. Data from vaccine manufacturers on Hib vaccine doses distributed in the United States were compared with trends in Hib disease incidence.

RESULTS:
The age-specific incidence of Hib disease among children less than 5 years old decreased by 71% from 37 per 100,000 persons in 1989 to 11 per 100,000 persons in 1991 (active surveillance data). Haemophilus influenzae meningitis incidence decreased by 82% between 1985 and 1991 (NBMRS data). Increases in doses of Hib vaccine distributed in the United States coincided with steep declines in Hib disease. Both surveillance systems showed decreased rates of Hib disease in infants less than 1 year old before vaccine was licensed for use in this age group. Haemophilus influenzae type b disease incidence in persons at least 12 years old and pneumococcal meningitis incidence in children less than 5 years old did not change substantially during the same period; therefore, decreased Hib disease in children less than 5 years old is not likely to be explained solely by changes in surveillance sensitivity or decreases in bacterial disease due to changes in medical practice.

CONCLUSION:
Our data suggest that conjugate vaccines have already had a marked impact on the incidence of Hib disease in the United States, preventing an estimated 10,000 to 16,000 cases of Hib disease in 1991. The decline of disease in infants less than 1 year old before licensure for this age group warrants further investigation.

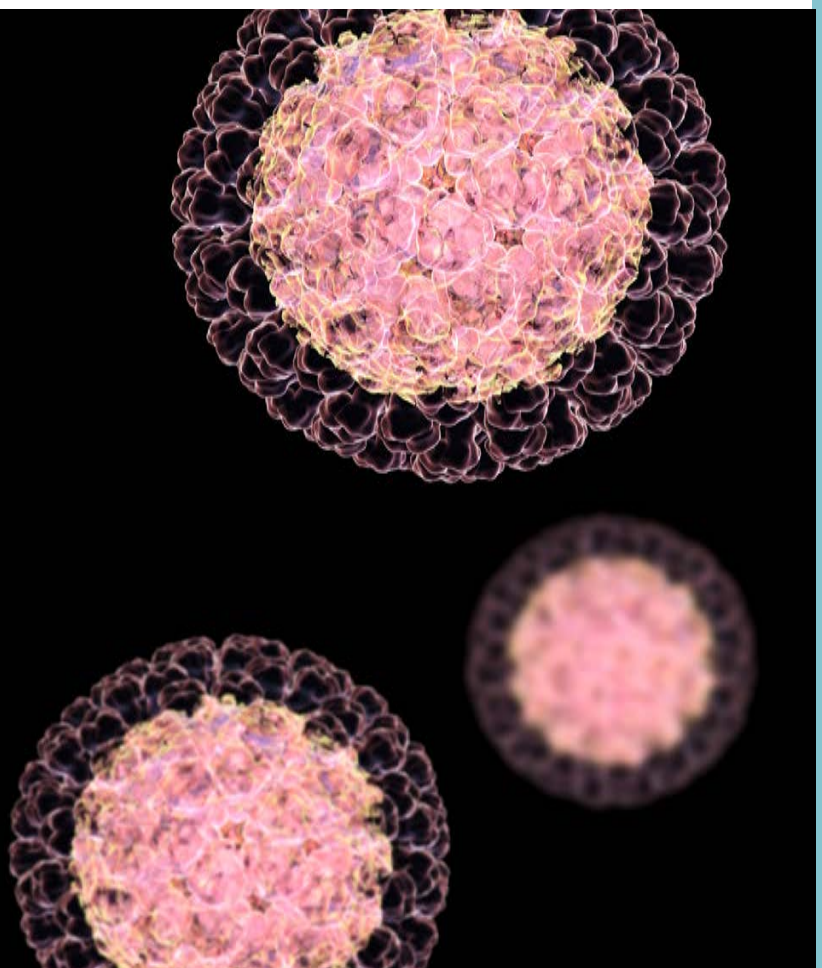
Citation:
Adams, William G. "Decline of Childhood Haemophilus Influenzae Type B (Hib) Disease in the Hib Vaccine Era." JAMA JAMA: The Journal of the American Medical Association 269.2 (1993)
https://pubmed.ncbi.nlm.nih.gov/8417239/



Discovery of rotavirus: Implications for Child health

Abstract

For centuries, acute diarrhea has been a major worldwide cause of death in young children, and until 1973, no infectious agents could be identified in about 80% of patients admitted to hospital with severe dehydrating diarrhea. In 1973 Ruth Bishop, Geoffrey Davidson, Ian Holmes, and Brian Ruck identified abundant particles of a 'new' virus (rotavirus) in the cytoplasm of mature epithelial cells lining duodenal villi and in feces, from such children admitted to the Royal Children's Hospital, Melbourne.



Rotaviruses have now been shown to cause 40-50% of severe acute diarrhea in young children worldwide in both developing and developed countries, and >600 000 young children die annually from rotavirus disease, predominantly in South- East Asia and sub-Saharan Africa. Longitudinal surveillance studies following primary infection in young children have shown that rotavirus reinfections are common. However the immune response that develops after primary infection is protective against severe symptoms on reinfection. This observation became the basis for development of live oral rotavirus vaccines. Two safe and effective vaccines are now licensed in 100 countries and in use in 17 countries (including Australia). Rotarix (GSK) is a single attenuated human rotavirus, representative of the most common serotype identified worldwide (G1P[8]). RotaTeq (Merck) is a pentavalent mixture of naturally attenuated bovine/human rotavirus reassortants representing G1, G2, G3, G4, and P(8) serotypes. Preliminary surveillance of the numbers of children requiring hospitalization for severe diarrhea, in USA, Brazil, and Australia, after introduction of these vaccines, encourages the hope that rotavirus infection need no longer be a threat to young children worldwide.

Citation:
Bishop, Ruth. "Discovery of Rotavirus: Implications for Child Health." Journal of Gastroenterology and Hepatology 24 (2009).
https://pubmed.ncbi.nlm.nih.gov/19799704/

Helmet therapy in infants with positional skull deformation: randomised controlled trial

Abstract

OBJECTIVE:
To determine the effectiveness of helmet therapy for positional skull deformation compared with the natural course of the condition in infants aged 5-6 months.

DESIGN:
Pragmatic, single blinded, randomised controlled trial (HEADS, HElmet therapy Assessment in Deformed Skulls) nested in a prospective cohort study.

SETTING:
29 paediatric physiotherapy practices; helmet therapy was administered at four specialised centres.

PARTICIPANTS:
84 infants aged 5 to 6 months with moderate to severe skull deformation, who were born after 36 weeks of gestation and had no muscular torticollis, craniosynostosis, or dysmorphic features. Participants were randomly assigned to helmet therapy (n=42) or to natural course of the condition (n=42) according to a randomisation plan with blocks of eight.

INTERVENTIONS:
Six months of helmet therapy compared with the natural course of skull deformation. In both trial arms parents were asked to avoid any (additional) treatment for the skull deformation.

MAIN OUTCOME MEASURES:
The primary outcome was change in skull shape from baseline to 24 months of age assessed using plagiocephalometry (anthropometric measurement instrument).

Change scores for plagiocephaly (oblique diameter difference index) and brachycephaly (craniproportional index) were each included in an analysis of covariance, using baseline values as the covariate. Secondary outcomes were ear deviation, facial asymmetry, occipital lift, and motor development in the infant, quality of life (infant and parent measures), and parental satisfaction and anxiety. Baseline measurements were performed in infants aged between 5 and 6 months, with follow-up measurements at 8, 12, and 24 months. Primary outcome assessment at 24 months was blinded.

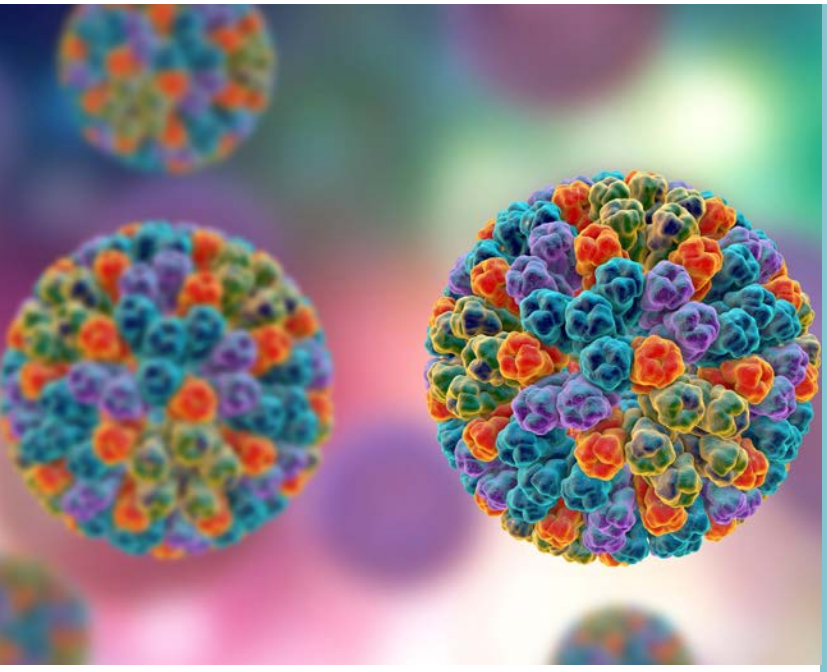
RESULTS:
The change score for both plagiocephaly and brachycephaly was equal between the helmet therapy and natural course groups, with a mean difference of −0.2 (95% confidence interval −1.6 to 1.2, P=0.80) and 0.2 (−1.7 to 2.2, P=0.81), respectively. Full recovery was achieved in 10 of 39 (26%) participants in the helmet therapy group and 9 of 40 (23%) participants in the natural course group (odds ratio 1.2, 95% confidence interval 0.4 to 3.3, P=0.74). All parents reported one or more side effects.

CONCLUSIONS:
Based on the equal effectiveness of helmet therapy and skull deformation following its natural course, high prevalence of side effects, and high costs associated with helmet therapy, we discourage the use of a helmet as a standard treatment for healthy infants with moderate to severe skull deformation.

Citation:
Wijk, R. M. Van, L. A. Van Vlimmeren, C. G. M. Groothuis-Oudshoorn, C. P. B. Van Der Ploeg, M. J. Ijzerman, and M. M. Boere-Boonekamp. "Helmet Therapy in Infants with Positional Skull Deformation: Randomised Controlled Trial." Bmj 348.May01 8 (2014)
http://www.bmj.com/content/348/bmj.g2741

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

Abstract



BACKGROUND:
International postlicensure studies have identified an increased risk of intussusception after vaccination with the second-generation rotavirus vaccines RotaTeq (RV5, a pentavalent vaccine) and Rotarix (RV1, a monovalent vaccine). We studied this association among infants in the United States.

METHODS:
The study included data from infants 5.0 to 36.9 weeks of age who were enrolled in three U.S. health plans that participate in the Mini-Sentinel program sponsored by the Food and Drug Administration. Potential cases of intussusception and vaccine exposures from 2004 through mid-2011 were identified through procedural and diagnostic codes. Medical records were reviewed to confirm the occurrence of intussusception and the status with respect to rotavirus vaccination. The primary analysis used a self-controlled risk-interval design that included only vaccinated children. The secondary analysis used a cohort design that included exposed and unexposed person-time.

RESULTS:
The analyses included 507,874 first doses and 1,277,556 total doses of RV5 and 53,638 first doses and 103,098 total doses of RV1. The statistical power for the analysis of RV1 was lower than that for the analysis of RV5. The number of excess cases of intussusception per 100,000 recipients of the first dose of RV5 was significantly elevated, both in the primary analysis (attributable risk, 1.1 [95% confidence interval, 0.3 to 2.7] for the 7-day risk window and 1.5 [95% CI, 0.2 to 3.2] for the 21-day risk window) and in the secondary analysis (attributable risk, 1.2 [95% CI, 0.2 to 3.2] for the 21-day risk window). No significant increase in risk was seen after dose 2 or 3. The results with respect to the primary analysis of RV1 were not significant, but the secondary analysis showed a significant risk after dose 2.

CONCLUSIONS:
RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients of the first dose. The secondary analysis of RV1 suggested a potential risk, although the study of RV1 was underpowered. These risks must be considered in light of the demonstrated benefits of rotavirus vaccination. (Funded by the Food and Drug Administration.)

Citations:
"Intussusception Risk after Rotavirus Vaccination in U.S. Infants." Child: Care, Health and Development Child Care Health Dev 40.3 (2014): 453. http://www.nejm.org/doi/full/10.1056/NEJMoa1303164#t=article

Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil

Abstract

BACKGROUND:
Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

METHODS:
We used case-series and case-control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

RESULTS:
We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case-control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico--an increase by a factor of 1.9 to 2.6 - was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.

CONCLUSIONS:
RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.).

Citations:
Perlman, Stanley. "Faculty of 1000 Evaluation for Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil." F1000 - Post-publication Peer Review of the Biomedical Literature
http://www.nejm.org/doi/full/10.1056/NEJMoa1012952#t=article

Melaleuca alternifolia (Tea Tree) Oil: a Review of Antimicrobial and Other Medicinal Properties

Abstract

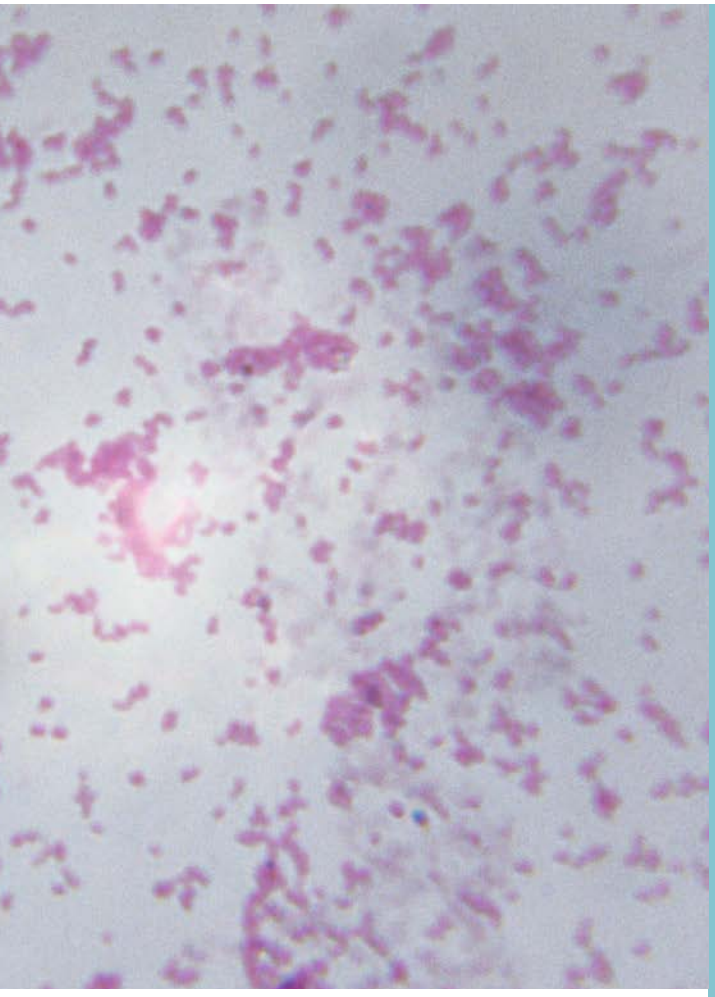
Complementary and alternative medicines such as tea tree (melaleuca) oil have become increasingly popular in recent decades. This essential oil has been used for almost 100 years in Australia but is now available worldwide both as neat oil and as an active component in an array of products. The primary uses of tea tree oil have historically capitalized on the antiseptic and anti-inflammatory actions of the oil. This review summarizes recent developments in our understanding of the antimicrobial and anti-inflammatory activities of the oil and its components, as well as clinical efficacy. Specific mechanisms of antimicrobial and anti-inflammatory action are reviewed, and the toxicity of the oil is briefly discussed.

Citations:
Carson, C. F., K. A. Hammer, and T. V. Riley. "Melaleuca Alternifolia (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." Clinical Microbiology Reviews 19.1 (2006): 50-62. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1360273/

DrPaulApproved

Parental Tdap Boosters and Infant Pertussis: A Case-Control Study

Abstract



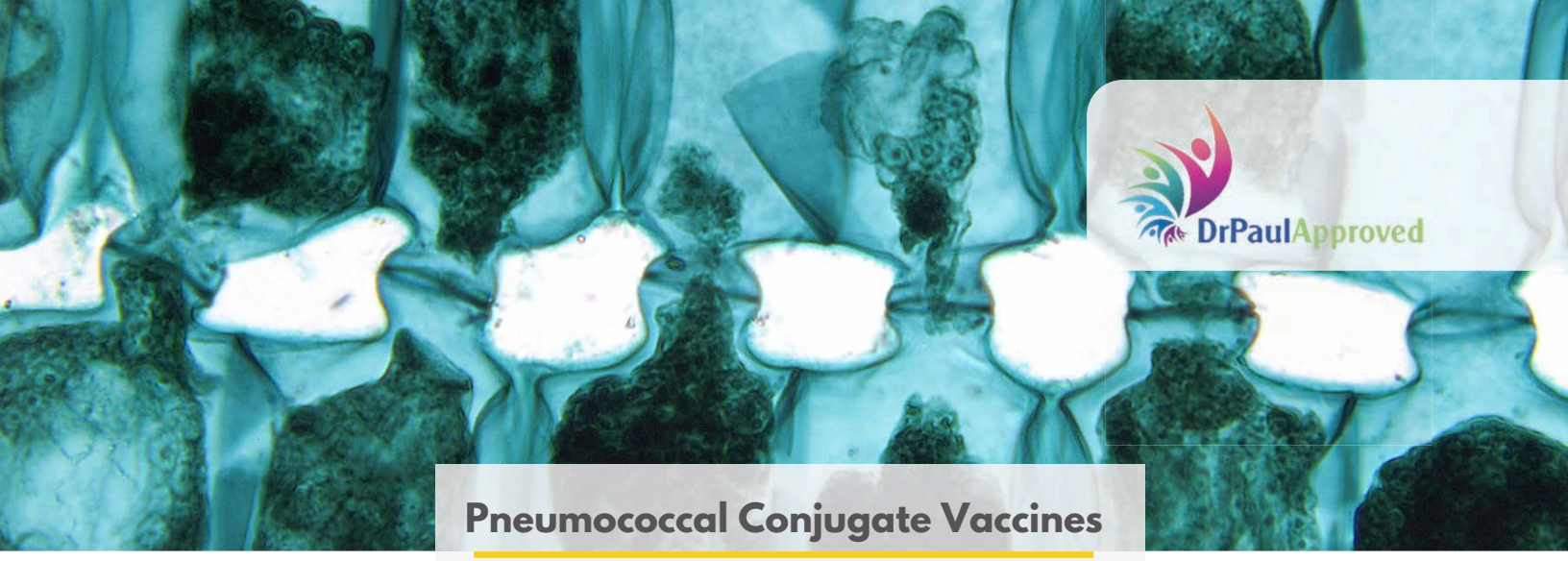
BACKGROUND:
Although recommended for almost a decade, evidence for field effectiveness of vaccinating close adult contacts of newborn infants against pertussis ("cocooning") is lacking. We evaluated the impact of a government-funded cocoon program during a pertussis epidemic in New South Wales, Australia.

METHODS:
We matched all New South Wales laboratory-confirmed pertussis cases aged <4 months with onset between April 1, 2009, to March 30, 2011 to controls from the state birth register by date of birth and area of residence. Parental vaccine receipt was by self-report, with a subset verified. Parents were considered "immunized" if vaccinated ⩾4 weeks before case symptom onset. The effectiveness of parental immunization (versus neither vaccinated) was quantified as (1 – odds ratio) × 100%.

RESULTS:
Case households had fewer immunized mothers (22% vs 32%) or fathers (20% vs 31%) but were more likely to include additional and older children. After adjustment, when both parents met our definition of immunized, risk of pertussis at<4 months of age was reduced by 51% (95% confidence interval 10% to 73%). Maternal vaccination prepregnancy and an immunized father reduced the risk by 51% (95% confidence interval 0% to 76%).

CONCLUSIONS:
Timely parental pertussis boosters provided significant protection. Evidence of protection from maternal vaccination prepregnancy is biologically plausible, and more precise data on the magnitude and duration of this is important for future policy recommendations.

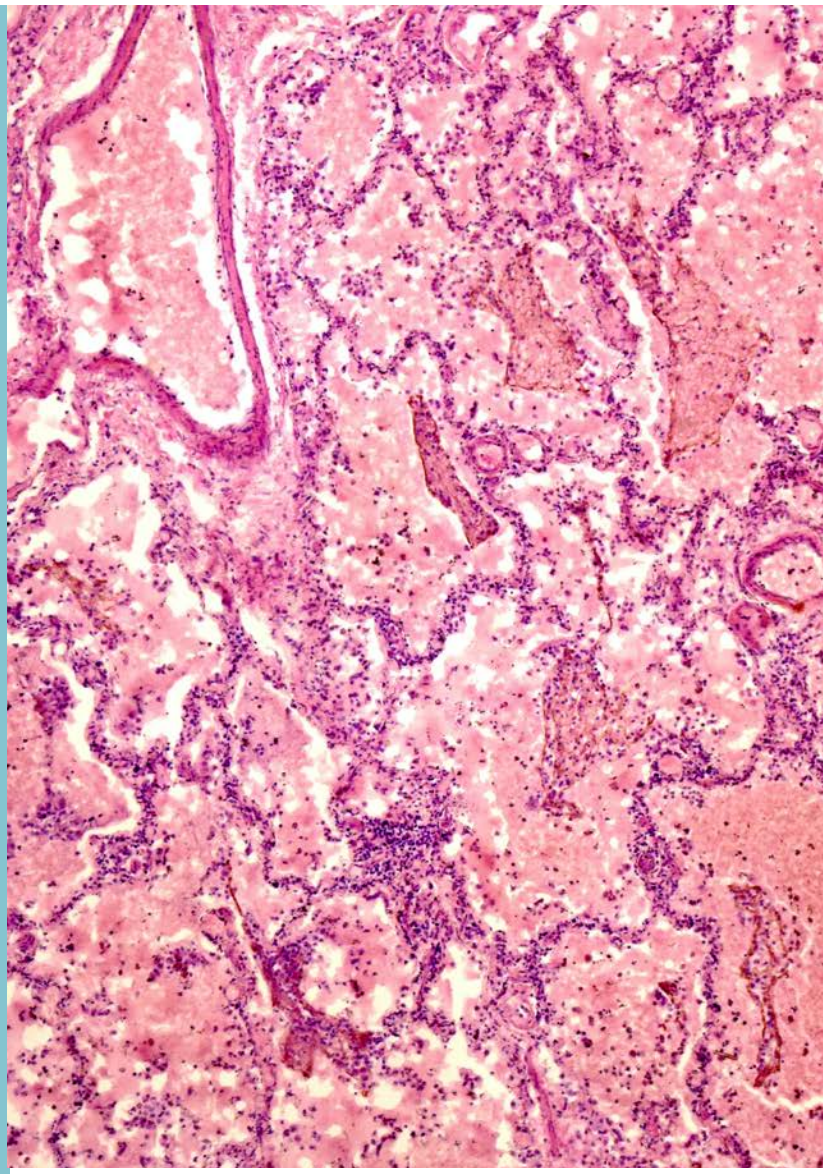
Citations:
"Parental Tdap Boosters and Infant Pertussis: A Case-Control Study." Pediatrics 134.4 (2014) 12.
http://pediatrics.aappublications.org/content/early/2014/09/09/peds.2014-1105



Pneumococcal Conjugate Vaccines

Abstract

Invasive infections caused by Streptococcus pneumoniae continue to be a major cause of morbidity and mortality worldwide, especially in children under 5 years of age. In the United States, 90% of invasive pneumococcal infections in children are caused by 13 serotypes of S. pneumoniae. The licensure (in 2000) and subsequent widespread use of a heptavalent pneumococcal conjugate vaccine (PCV7) have had a significant impact on decreasing the incidence of serious invasive pneumococcal disease (IPD) in all age groups, especially in children under 2 years of age. However, the emergence of replacement non-PCV7 serotypes, especially serotype 19A, has resulted in an increase in the incidence of serious and invasive infections. In 2010, a 13-valent PCV was licensed in the United States. However, the impact that this vaccine will have on IPD remains to be seen. The objectives of this review are to discuss the epidemiology of serious and invasive pneumococcal infections in the United States in the PCV era and to review some of the pneumococcal vaccines that are in development.



Citations:
Disease in the United States in the Era of Pneumococcal Conjugate Vaccines." Clinical Microbiology Reviews 25.3 (2012)
http://www.ncbi.nlm.nih.gov/pubmed/22763632

Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic

Abstract

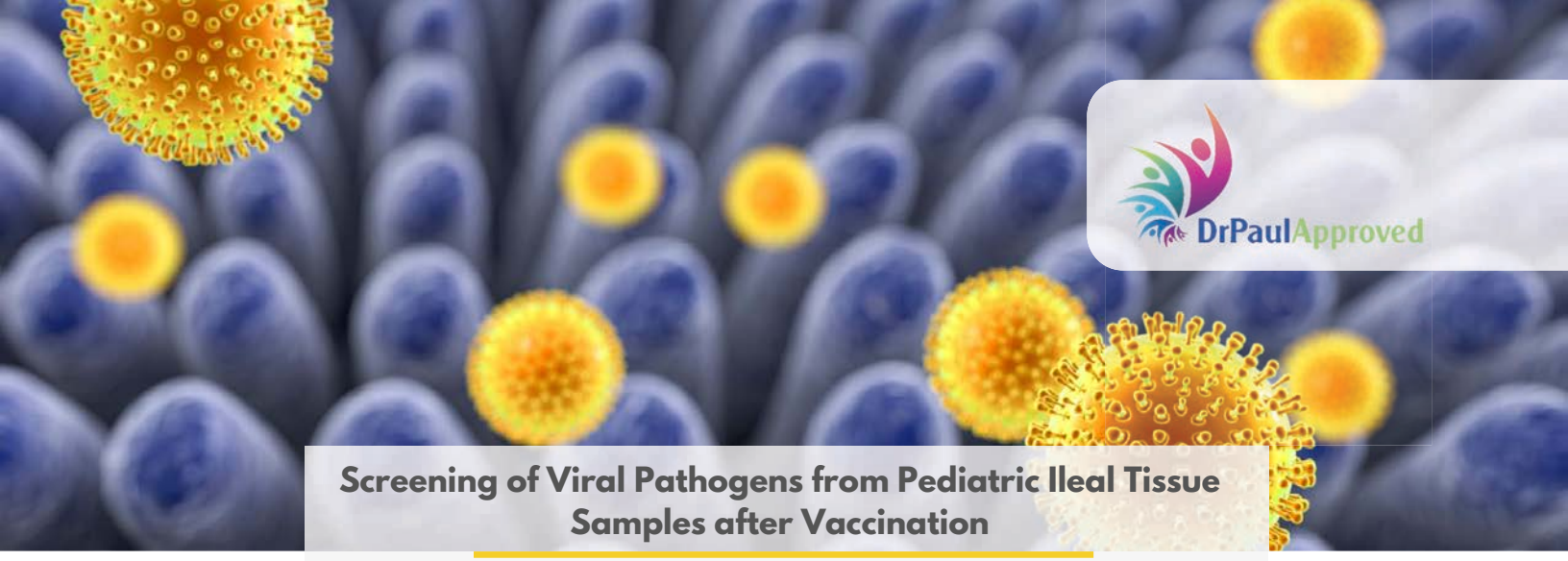
BACKGROUND:
Acellular pertussis vaccines replaced whole-cell vaccines for the 5-dose childhood vaccination series in 1997. A sixth dose of pertussis-containing vaccine, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap), was recommended in 2005 for adolescents and adults. Studies examining Tdap vaccine effectiveness (VE) among adolescents who have received all acellular vaccines are limited.

METHODS:
To assess Tdap VE and duration of protection, we conducted a matched case-control study during the 2012 pertussis epidemic in Washington among adolescents born during 1993–2000. All pertussis cases reported from January 1 through June 30, 2012, in 7 counties were included; 3 controls were matched by primary provider clinic and birth year to each case. Vaccination histories were obtained through medical records, the state immunization registry, and parent interviews. Participants were classified by type of pertussis vaccine received on the basis of birth year: a mix of whole-cell and acellular vaccines (1993–1997) or all acellular vaccines (1998– 2000). We used conditional logistic regression to calculate odds ratios comparing Tdap receipt between cases and controls.

RESULTS:
Among adolescents who received all acellular vaccines (450 cases, 1246 controls), overall Tdap VE was 63.9% (95% confidence interval [CI]: 50% to 74%). VE within 1 year of vaccination was 73% (95% CI: 60% to 82%). At 2 to 4 years postvaccination, VE declined to 34% (95% CI: −0.03% to 58%).

CONCLUSIONS:
Tdap protection wanes within 2 to 4 years. Lack of long-term protection after vaccination is likely contributing to increases in pertussis among adolescents.

Citation:
"Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic." Pediatrics 135.6 (2015) http://pediatrics.aappublications.org/content/early/2015/04/28/peds.2014-3358



Screening of Viral Pathogens from Pediatric Ileal Tissue Samples after Vaccination

Abstract

In 2010, researchers reported that the two US-licensed rotavirus vaccines contained DNA or DNA fragments from porcine circovirus (PCV). Although PCV, a common virus among pigs, is not thought to cause illness in humans, these findings raised several safety concerns. In this study, we sought to determine whether viruses, including PCV, could be detected in ileal tissue samples of children vaccinated with one of the two rotavirus vaccines. A broad spectrum, novel DNA detection technology, the Lawrence Livermore Microbial Detection Array (LLMDA), was utilized, and confirmation of viral pathogens using the polymerase chain reaction (PCR) was conducted. The LLMDA technology was recently used to identify PCV from one rotavirus vaccine. Ileal tissue samples were analyzed from 21 subjects, aged 15–62 months. PCV was not detected in any ileal tissue samples by the LLMDA or PCR. LLMDA identified a human rotavirus A from one of the vaccinated subjects, which is likely due to a recent infection from a wild type rotavirus. LLMDA also identified human parechovirus, a common gastroenteritis viral infection, from two subjects. Additionally, LLMDA detected common gastrointestinal bacterial organisms from the Enterobacteriaceae, Bacteroidaceae, and Streptococcaceaefamilies from several subjects. This study provides a survey of viral and bacterial pathogens from pediatric ileal samples, and may shed light on future studies to identify pathogen associations with pediatric vaccinations.

Citation:
Hewitson, Laura, James B. Thissen, Shea N. Gardner, Kevin S. Mcloughlin, Margaret K. Glausser, and Crystal J. Jaing. "Screening of Viral Pathogens from Pediatric Ileal Tissue Samples after Vaccination." Advances in Virology 2014 (2014): 1-10.
http://www.hindawi.com/journals/av/2014/720585/

DrPaulApproved

The Incidence of Positional Plagiocephaly: A Cohort Study

Abstract

OBJECTIVE:
The objective of this study was to estimate the incidence of positional plagiocephaly in infants 7 to 12 weeks of age who attend the 2-month well-child clinic in Calgary, Alberta, Canada.

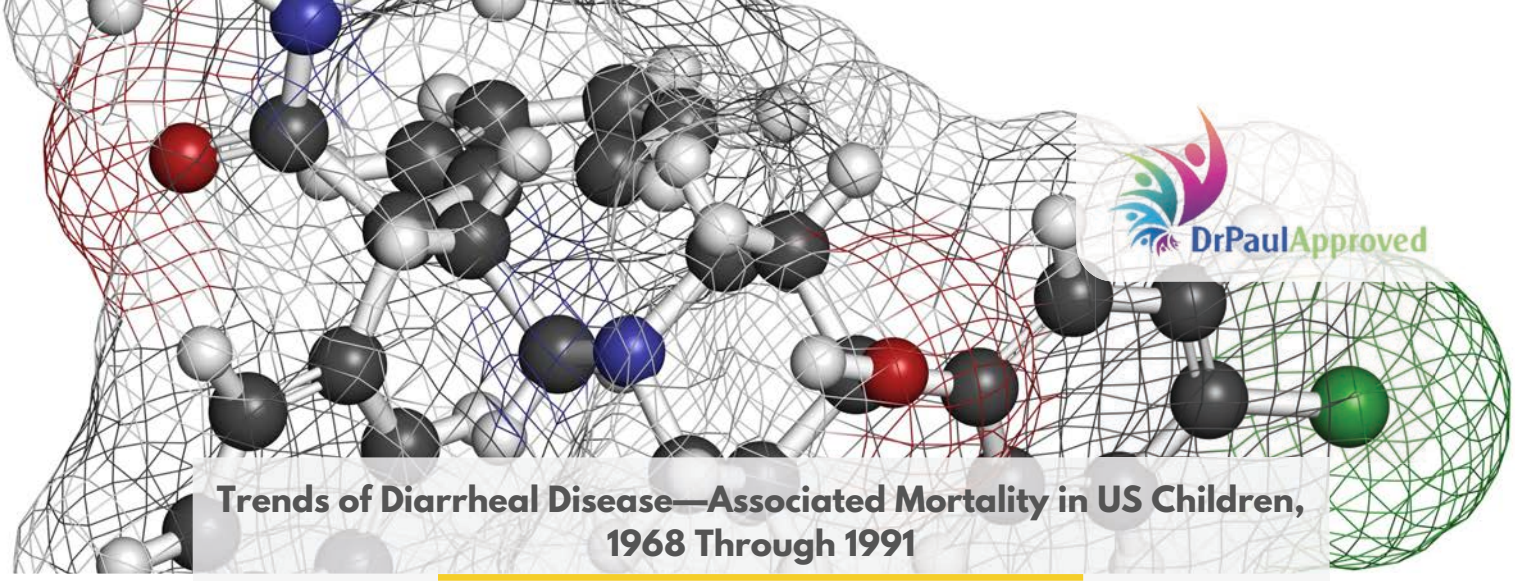
METHODS:
A prospective cohort design was used to recruit 440 healthy full-term infants (born at ⩾37 weeks of gestation) who presented at 2-month well-child clinics for public health nursing services (eg, immunization) in the city of Calgary, Alberta.

The study was completed in 4 community health centers (CHCs) from July to September 2010. The CHCs were selected based on their location, each CHC representing 1 quadrant of the city. Argenta's (2004) plagiocephaly assessment tool was used to identify the presence or absence of plagiocephaly.

RESULTS:
Of the 440 infants assessed, 205 were observed to have some form of plagiocephaly. The incidence of plagiocephaly in infants at 7 to 12 weeks of age was estimated to be 46.6%. Of all infants with plagiocephaly, 63.2% were affected on the right side and 78.3% had a mild form.

CONCLUSIONS:
To our knowledge, this is the first population-based study to investigate the incidence of positional plagiocephaly using 4 community-based data collection sites. Future studies are required to corroborate the findings of our study. Research is required to assess the incidence of plagiocephaly using Argenta's plagiocephaly assessment tool across more CHCs and to assess prevalence at different infant age groups. The utility of using Argenta's plagiocephaly assessment tool by public health nurses and/or family physicians needs to be established.

Citation:
"The Incidence of Positional Plagiocephaly: A Cohort Study." Pediatrics 132.2 (2013)
http://pediatrics.aappublications.org/content/early/2013/07/02/peds.2012-3438



Trends of Diarrheal Disease—Associated Mortality in US Children, 1968 Through 1991

Abstract

OBJECTIVES:
To describe temporal patterns in mortality related to diarrheal disease in US children and to assess progress toward its prevention and control.

DESIGN:
Retrospective analyses of death certificate data on diarrhea of all causes compiled by the National Center for Health Statistics, Centers for Disease Control and Prevention, Atlanta, Ga.

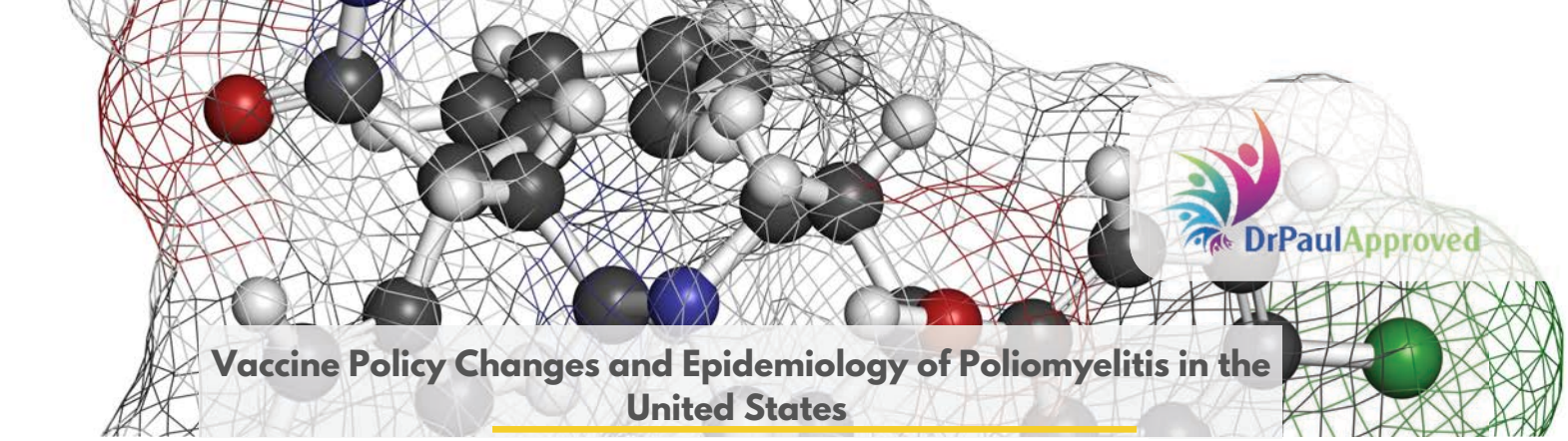
PATIENTS:
Children aged 1 month through 4 years who died with diarrhea.

SETTING:
United States, 1968 through 1991.

RESULTS:
A total of 14137 deaths associated with diarrhea among children were reported in the United States between 1968 and 1991. Of these, 78% occurred in infants (ie, aged 1 to 11 months); the median age at the time of death has declined from 5 to 1.5 months. Diarrheal disease mortality dropped by approximately 75% during the first 18 years of the study, but no decline has occurred since 1985. Infant mortality due to diarrhea (per 100 000 live births) averaged 12.8 and was found to be high for blacks (33.1) and for residents of the southern United States (18.5). The infant mortality due to diarrhea from 1986 through 1991 is 5.9. Peaks in winter deaths previously associated with rotavirus were prominent in the early years among infants aged 4 through 11 months. Such peaks have virtually disappeared since 1985. Diarrhea was the principal cause of death, as the leading associated diagnoses (electrolyte disorders [30%], cardiac arrest [16%], shock [8%], and nausea/vomiting [4%]) were commonly recognized complications of diarrhea. Since 1979, prematurity has emerged as a common associated diagnosis.

CONCLUSIONS:
Diarrheal deaths nationwide have declined 75% from 1968 to 1985 but stabilized since then at about 300 deaths per year. Because many of these deaths may still be preventable by early rehydration, future prevention efforts should be directed at educating health care providers about the continuing problem and recognition of the high-risk infant and at teaching mothers of such infants to begin rehydration early and to seek medical attention when their infant develops diarrhea.(JAMA. 1995;274:1143-1148)

Citation:
Kilgore, P. E. "Trends of Diarrheal Disease--associated Mortality in US Children, 1968 through 1991." JAMA: The Journal of the American Medical Association 274.14 (1995): 1143- 148.
http://jama.jamanetwork.com/article.aspx?articleid=389779



Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States

Abstract

CONTEXT:
The last case of poliomyelitis in the United States due to indigenously acquired wild poliovirus occurred in 1979; however, as a consequence of oral poliovirus vaccine (OPV) use that began in 1961, an average of 9 cases of vaccine-associated paralytic poliomyelitis (VAPP) were confirmed each year from 1961 through 1989. To reduce the VAPP burden, national vaccination policy changed in 1997 from reliance on OPV to options for a sequential schedule of inactivated poliovirus vaccine (IPV) followed by OPV. In 2000, an exclusive IPV schedule was adopted.

OBJECTIVE:
To review the epidemiology of paralytic poliomyelitis and document the association between the vaccine schedule changes and VAPP in the United States.

DESIGN & SETTING:
Review of national surveillance data from 1990 through 2003 for cases of confirmed paralytic poliomyelitis.

MAIN OUTCOME MEASURES:
Number of confirmed paralytic poliomyelitis cases, including VAPP, and ratio of VAPP cases to number of doses of OPV distributed that occurred before, during, and after implementation of policy changes.

RESULTS:
From 1990 through 1999, 61 cases of paralytic poliomyelitis were reported; 59 (97%) of these were VAPP (1 case per 2.9 million OPV doses distributed), 1 case was imported, and 1 case was indeterminate. Thirteen cases occurred during the 1997-1999 transitional policy period and were associated with the all-OPV schedule; none occurred with the IPV-OPV schedule. No cases occurred after the United States implemented the all-IPV policy in 2000. The last imported poliomyelitis case occurred in 1993 and the last case of VAPP occurred in 1999.

CONCLUSIONS:
The change in polio vaccination policy from OPV to exclusive use of IPV was successfully implemented; this change led to the elimination of VAPP in the United States.

In 1952, 3 years before the licensure of the first poliomyelitis vaccine, more than 21 000 cases of paralytic poliomyelitis were documented in the United States.1 The use of inactivated poliovirus vaccine (IPV) and, later, oral poliovirus vaccine (OPV) led to a precipitous drop in reported cases of poliomyelitis.2

The last cases of poliomyelitis caused by indigenously acquired wild poliovirus occurred in 1979 during an outbreak following importation from Canada.3 Genetic studies of poliovirus isolates from the 1970s suggested that endemic circulation of wild polioviruses in the United States may have ceased by the late 1960s, and subsequent sporadic cases and small outbreaks due to wild poliovirus during the 1970s probably represented importations from neighboring countries.4

Citation:
Alexander, Lorraine Niño. "Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States." Jama 292.14 (2004): 1696.
http://jama.jamanetwork.com/article.aspx?articleid=199583

Monovalent OPV type 3 became available in 1961 in the United States. Trivalent OPV (offering protection against the 3 poliovirus serotypes) was licensed in the United States in 1963 and became the vaccine of choice for prevention of poliomyelitis in the United States and most of the world.5 Oral poliovirus vaccine was considered superior to IPV because of provision of better intestinal immunity, ability to indirectly vaccinate susceptible contacts through transmission of vaccine polioviruses, ease of administration, and lower costs. However, a serious consequence of the use of this live- virus vaccine, vaccine-associated paralytic poliomyelitis (VAPP), was recognized as early as 1962.6,7 From 1961 through 1989, an average of 9 cases of VAPP (range, 1-25 cases) were confirmed each year.8- 10

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In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000.11 Universal implementation of polio eradication strategies substantially reduced the risk of poliovirus importation into the United States.12 In response to the changing risk-benefit profile associated with OPV use, the Institute of Medicine conducted independent evaluations on polio vaccine policy options in the United States in 1977 and 1988,13,14 and in 1995,

participated in a policy review initiated by the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices.15 The discussion of changing reliance from OPV to IPV led to national debates in the mid 1990s.16 It was thought that the potential for reduced compliance due to higher costs and the increased number of injections associated with IPV, coupled with possible reduced mucosal immunity in IPV recipients, could lead to wild poliovirus outbreaks.17,18

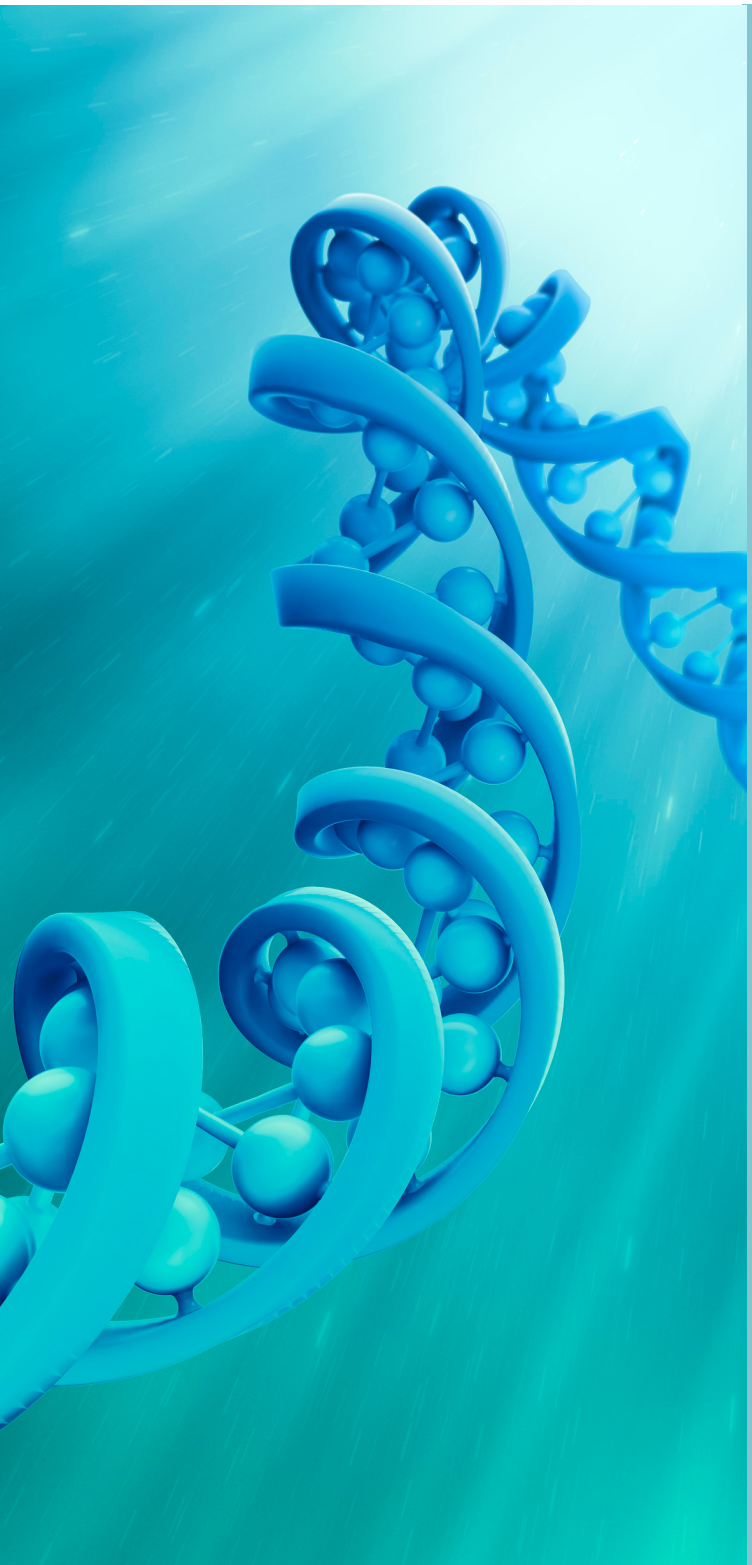
However, as the likelihood of wild poliovirus importations declined, the risk of VAPP with routine use of OPV became more difficult to justify. In June 1996, a policy change was made when the Advisory Committee on Immunization Practices recommended a transition to IPV by first introducing a sequential vaccination schedule of 2 doses of IPV followed by 2 doses of OPV.17 This schedule was predicted to reduce the number of VAPP cases by 53%, with the greatest impact on recipients.19 However, more flexible policy options were supported by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) that allowed for an all-OPV schedule or an all-IPV schedule, provided parents were educated about the decision.18,20 In January 1999, the AAP and AAFP revised their recommendations to state that only IPV should be administered for doses 1 and 2, citing that VAPP continued to be associated with the all-OPV schedule21 and that the vaccine options were not always presented to patients and parents.20 Further progress toward global polio eradication and the desire to eliminate VAPP prompted all policy-setting groups to recommend that an all- IPV schedule be implemented in 2000.22,23

This report reviews national poliomyelitis surveillance data in the United States from 1990 through 2003, describes the epidemiology of poliomyelitis, and assesses the impact of the poliomyelitis vaccine policy changes on the occurrence of paralytic poliomyelitis in the United States.

Citation:
Alexander, Lorraine Niño. "Vaccine Policy Changes and Epidemiology of Poliomyelitis in the United States." Jama 292.14 (2004): 1696.
http://jama.jamanetwork.com/article.aspx?articleid=199583

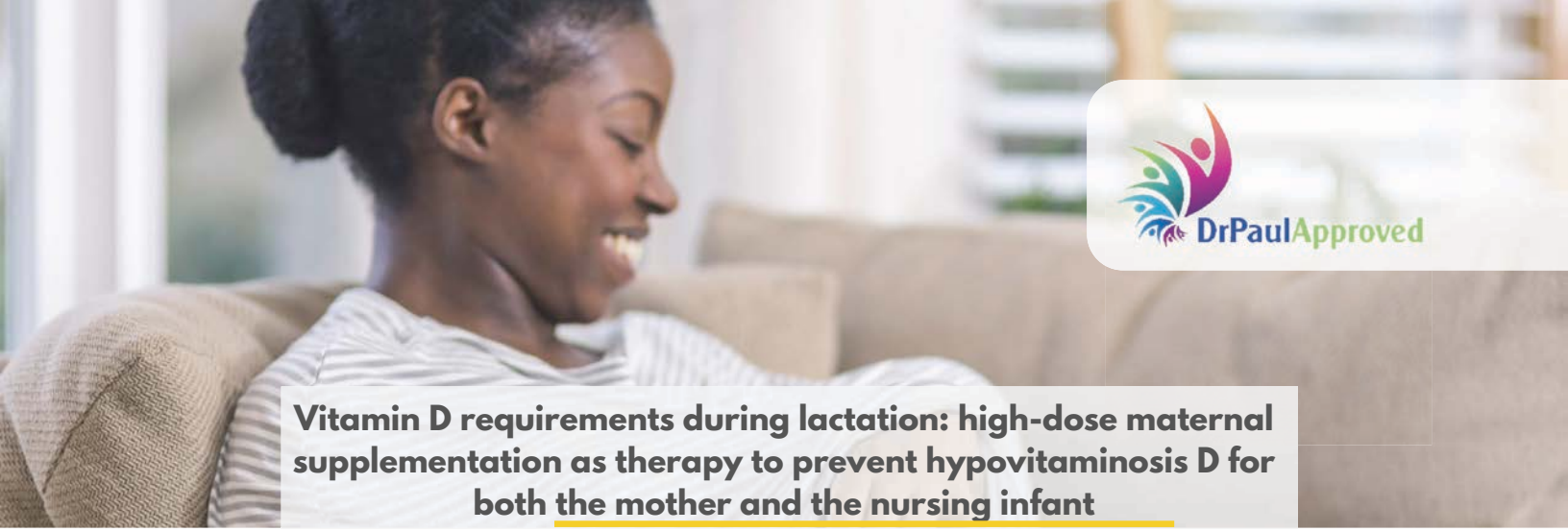
Viral nucleic acids in live-attenuated vaccines: detection of minority variants and an adventitious virus

Abstract



Metagenomics and a panmicrobial microarray were used to examine eight live-attenuated viral vaccines. Viral nucleic acids in trivalent oral poliovirus (OPV), rubella, measles, yellow fever, varicella-zoster, multivalent measles/mumps/rubella, and two rotavirus live vaccines were partially purified, randomly amplified, and pyrosequenced. Over half a million sequence reads were generated covering from 20 to 99% of the attenuated viral genomes at depths reaching up to 8,000 reads per nucleotides. Mutations and minority variants, relative to vaccine strains, not known to affect attenuation were detected in OPV, mumps virus, and varicella-zoster virus. The anticipated detection of endogenous retroviral sequences from the producer avian and primate cells was confirmed. Avian leukosis virus (ALV), previously shown to be noninfectious for humans, was present as RNA in viral particles, while simian retrovirus (SRV) was present as genetically defective DNA. Rotarix, an orally administered rotavirus vaccine, contained porcine circovirus-1 (PCV1), a highly prevalent nonpathogenic pig virus, which has not been shown to be infectious in humans. Hybridization of vaccine nucleic acids to a panmicrobial microarray confirmed the presence of endogenous retroviral and PCV1 nucleic acids. Deep sequencing and microarrays can therefore detect attenuated virus sequence changes, minority variants, and adventitious viruses and help maintain the current safety record of live-attenuated viral vaccines.

Citation:
Victoria, J. G., C. Wang, M. S. Jones, C. Jaing, K. Mcloughlin, S. Gardner, and E. L. Delwart. "Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus." Journal of Virology 84.12 (2010): 6033-040. http://www.ncbi.nlm.nih.gov/pubmed/20375174



Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant

Abstract

Scientific data pertaining to vitamin D supplementation during lactation are scarce. The daily recommended intake for vitamin D during lactation has been arbitrarily set at 400 IU/d (10 microg/d). This recommendation is irrelevant with respect to maintaining the nutritional vitamin D status of mothers and nursing infants, especially among darkly pigmented individuals. Our objective was to examine the effect of high-dose maternal vitamin D2 supplementation on the nutritional vitamin D status of mothers and nursing infants. Fully lactating women (n =18) were enrolled at 1 mo after birth to 1 of 2 treatment arms, ie, 1600 IU vitamin D2 and 400 IU vitamin D3 (prenatal vitamin) or 3600 IU vitamin D2 and 400 IU vitamin D3, for a 3-mo study period. High-dose (1600 or 3600 IU/d) vitamin D2 supplementation for a period of 3 mo safely increased circulating 25-hydroxyvitamin D [25(OH)D] concentrations for both groups. The antirachitic activity of milk from mothers receiving 2000 IU/d vitamin D increased by 34.2 IU/L, on average, whereas the activity in the 4000 IU/d group increased by 94.2 IU/L. Nursing infant circulating 25(OH)D2 concentrations reflected maternal intake and the amount contained in the milk. With limited sun exposure, an intake of 400 IU/d vitamin D would not sustain circulating 25(OH)D concentrations and thus would supply only limited amounts of vitamin D to nursing infants in breast milk. A maternal intake of 4000 IU/d could achieve substantial progress toward improving both maternal and neonatal nutritional vitamin D status.

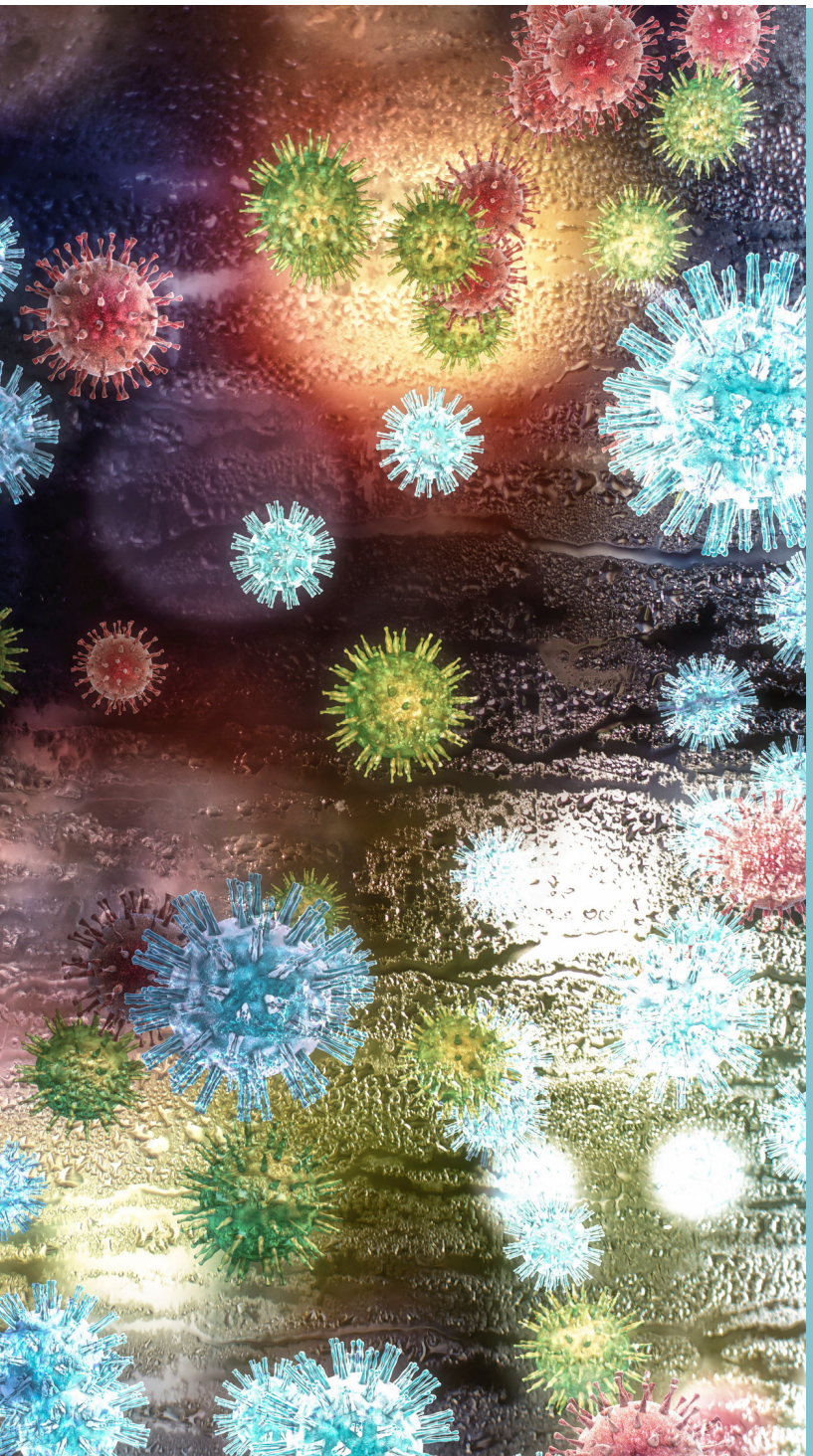
Citation:
"Maternal Versus Infant Vitamin D Supplementation During Lactation: A Randomized Controlled Trial." Pediatrics 136.4 (2015)
http://www.ncbi.nlm.nih.gov/pubmed/15585800

CHAPTER 6

DrPaulApproved

Adverse Effects of Aspirin, Acetaminophen, and Ibuprofen on Immune Function, Viral Shedding, and Clinical Status in Rhinovirus-Infected Volunteers

Abstract



A double-blind, placebo-controlled trial was conducted to study the effects of over-the-counter analgesic/antipyretic medications on virus shedding, immune response, and clinical status in the common cold. Sixty healthy volunteers were challenged intranasally with rhinovirus type 2 and randomized to one of four treatment arms: aspirin, acetaminophen, ibuprofen, or placebo. Fifty- six volunteers were successfully infected and shed virus on at least 4 days after challenge. Virus shedding, antibody levels, clinical symptoms and signs, and blood leukocyte levels were carefully monitored. Use of aspirin and acetaminophen was associated with suppression of serum neutralizing antibody response (P less than .05 vs. placebo) and increased nasal symptoms and signs (P less than .05 vs. placebo). A concomitant rise in circulating monocytes suggested that the suppression of antibody response may be mediated through drug effects on monocytes and/or mononuclear phagocytes. There were no significant differences in viral shedding among the four groups, but a trend toward longer duration of virus shedding was observed in the aspirin and acetaminophen groups."nursing infants in breast milk.

Citation:
Burgess, Jeff. "Adverse Effects of Aspirin, Acetaminophen, and Ibuprofen on Immune Function, Viral Shedding, and Clinical Status in Rhinovirus-infected Volunteers." Annals of Emergency Medicine 20.7 (1991): 823.
http://www.ncbi.nlm.nih.gov/pubmed/2172402

Are Well-child Visits a Risk Factor for Subsequent InfluenzaLike-Illness Visits?

Abstract

To determine whether well-child visits are a risk factor for subsequent influenza-like illness (ILI) visits within a child's family.

DESIGN:
Retrospective cohort.

METHODS:
Using data from the Medical Expenditure Panel Survey from the years 1996-2008, we identified 84,595 families. For each family, we determined those weeks in which a well- child visit or an ILI visit occurred. We identified 23,776 well-child-visit weeks and 97,250 ILI-visit weeks. We fitted a logistic regression model, where the binary dependent variable indicated an ILI clinic visit in a particular week. Independent variables included binary indicators to denote a well-child visit in the concurrent week or one of the previous 2 weeks, the occurrence of the ILI visit during the influenza season, and the presence of children in the family in each of the age groups 0-3, 4- 7, and 8-17 years. Socioeconomic variables were also included. We also estimated the overall cost of well-child-exam-related ILI using data from 2008.

RESULTS:
We found that an ILI office visit by a family member was positively associated with a well-child visit in the same or one of the previous 2 weeks (odds ratio, 1.54). This additional risk translates to potentially 778,974 excess cases of ILI per year in the United States, with a cost of $500 million annually.

CONCLUSIONS:
Our results should encourage ambulatory clinics to strictly enforce infection control recommendations. In addition, clinics could consider time-shifting of well-child visits so as not to coincide with the peak of the influenza season.

Citation:
Simmering, Jacob E., Linnea A. Polgreen, Joseph E. Cavanaugh, and Philip M. Polgreen. "Are Well-Child Visits a Risk Factor for Subsequent Influenza-Like Illness Visits?" Infect Control Hosp Epidemiol Infection Control & Hospital Epidemiology 35.03 (2014): 251- 56.
http://www.ncbi.nlm.nih.gov/pubmed/24521589

Association between Breastfeeding and Intelligence, Educational Attainment, and Income at 30 Years of Age: A Prospective Birth Cohort Study from Brazil

Abstract

BACKGROUND:
Breastfeeding has clear short-term benefits, but its long-term consequences on human capital are yet to be established. We aimed to assess whether breastfeeding duration was associated with intelligence quotient (IQ), years of schooling, and income at the age of 30 years, in a setting where no strong social patterning of breastfeeding exists.

METHODS:
A prospective, population-based birth cohort study of neonates was launched in 1982 in Pelotas, Brazil. Information about breastfeeding was recorded in early childhood. At 30 years of age, we studied the IQ (Wechsler Adult Intelligence Scale, 3rd version), educational attainment, and income of the participants. For the analyses, we used multiple linear regression with adjustment for ten confounding variables and the G-formula.

FINDINGS:
From June 4, 2012, to Feb 28, 2013, of the 5914 neonates enrolled, information about IQ and breastfeeding duration was available for 3493 participants. In the crude and adjusted analyses, the durations of total breastfeeding and predominant breastfeeding (breastfeeding as the main form of nutrition with some other foods) were positively associated with IQ, educational attainment, and income. We identified dose-response associations with breastfeeding duration for IQ and educational attainment. In the confounder-adjusted analysis, participants who were breastfed for 12 months or more had higher IQ scores (difference of 3·76 points, 95% CI 2·20– 5·33), more years of education (0·91 years, 0·42–1·40), and higher monthly incomes (341·0 Brazilian reals, 93·8–588·3) than did those who were breastfed for less than 1 month. The results of our mediation analysis suggested that IQ was responsible for 72% of the effect on income.

INTERPRETATION:
Breastfeeding is associated with improved performance in intelligence tests 30 years later, and might have an important effect in real life, by increasing educational attainment and income in adulthood.

Citation:
Victora, Cesar G., Bernardo Lessa Horta, Christian Loret De Mola, Luciana Quevedo, Ricardo Tavares Pinheiro, Denise P. Gigante, Helen Gonçalves, and Fernando C. Barros. "Association between Breastfeeding and Intelligence, Educational Attainment, and Income at 30 Years of Age: A Prospective Birth Cohort Study from Brazil." The Lancet Global Health 3.4 (2015). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998971/

Breastfeeding and Health Outcomes Article

Abstract

I HAVE THE GOOD FORTUNE to work at the Agency for Health Care Research and Quality (AHRQ), where I have the opportunity to help translate numbers and evidence into meaningful action to improve health and health care. In my work I am privileged to support the U.S. Preventive Services Task Force and collaborate with and fund researchers in primary care. The mission of the Agency is to improve the quality, safety, effectiveness, and efficiency of health care for all Americans. Today, I'm going to talk about the effects of breastfeeding on the health of women and children.

When we deconstruct breastfeeding to identify its effects on individual healthcare outcomes, we lose the bigger picture. Breastfeeding is a dynamic, complex, living practice—a multidimensional, relational system involving not only a mother and child, but their entire environment. I generally approach breastfeeding as a means of optimizing a child's chances for reaching his or her full potential. This sometimes creates conflict, because breastfeeding is not the magic guarantee for well-being that physicians and policy makers sometimes want. It is also important to remember that an individual family, making a decision about helping the development of a child, has a perspective on breastfeeding that is very different from the viewpoint of the population at large and of the policy makers who monitor public concerns.

To set a foundation for this summit, I am pleased to be able to summarize a report published in 2007 on outcomes of breastfeeding on maternal and infant health in developed countries that was prepared for AHRQ by the Evidence-Based Practice Center (EPC) of the Tufts–New England Medical Center, Boston, MA.

The EPC program was established by AHRQ in 1997 to review all relevant scientific literature on clinical, behavioral, and organization and financing topics to produce evidence reports and technology assessments. EPC evidence reports are based on rigorous, comprehensive syntheses and analyses of the scientific literature. There are currently 14 centers around the United States and Canada that are commissioned to systematically review the evidence surrounding a particular practice. The methodology used by the EPC is very explicit; its documentation is very detailed. The EPCs collaborate broadly with experts around the world in various fields to produce reports on aspects of healthcare practice and outcomes that policy makers as well as clinicians use to guide health care.

The EPC's 2007 report on breastfeeding in maternal and infant health summarized evidence through May 2006 from different types of studies in the English-language literature, including randomized controlled trials and controlled observational studies. Over 9,000 articles were considered for this report. Given the breath of literature, the EPC relied on previously conducted systematic reviews and meta-analysis and at times conducted new and updated meta-analysis as well. Every study was examined and graded for its methodologic quality, and some studies of poorer quality were discarded.

Citation:
Meyers, David. "Breastfeeding and Health Outcomes." Breastfeeding Medicine 4.S1 (2009) 5.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998971/

The 2007 EPC report concluded that breastfeeding provided short-term benefits for infants in terms of a lower frequency of common illnesses, including ear infections and vomiting and diarrhea. The evidence suggests that for every six children who are breastfed exclusively for the first 6 months of life, one of them will not have an ear infection that he or she would otherwise have had. That means that of the approximately 4 million infants born in the United States every year, 2 million would be expected to have an ear infection in the first 6 months of life. If breastfeeding rates in America were increased to 80% of children, there would be 300,000 fewer ear infections than there now are. Among formula-fed infants the incidence of vomiting and diarrhea is nearly 100% in the first year of life, as compared with such illness in fewer than half of breastfed children.

The report found that the benefits are not only for common illnesses that occur in infancy, but also for rarer but serious illnesses. The rates of hospitalizations for pneumonia and severe lower respiratory tract infection are lower among breastfed infants than among those not breastfed. A meta-analysis found a significant inverse association between breastfeeding and sudden infant death syndrome (SIDS).

The benefits of breastfeeding are not limited to infancy; they extend into childhood and even into adulthood. A history of breastfeeding is clearly associated with decreased rates of common conditions, including eczema and obesity, and decreased rates of serious diseases, including type 2 diabetes and childhood leukemias.

When considering the benefits of breastfeeding, or more accurately the risks of not breastfeeding, I think it is helpful to put the numbers into context. [Note that slides presented along with this talk included odds ratios taken from the 2007 EPC report.]

To help provide this context, I want to introduce the concept of the "number needed to treat," which refers to the number of people to whom a treatment or technique must be applied in order for it to make an effective difference in health.

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Suppose a patient comes into my office with a sprained ankle, and I decide to prescribe a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen or ibuprofen to ease the patient's pain. Most of us assume that if we take a pain killer we are almost certainly going to get good pain relief. If you look at the evidence for this treatment, however, you find that NSAIDs provide effective relief for only one of every two people; 50% of the people for whom it is used do not get significant relief. We say therefore that on average we need to treat two people for one person to get good relief. NSAIDS for pain relief from sprains has a number-needed-to-treat of 2.

The effects of antibiotics on ear infections are likewise surprising, with only one in seven children in the United States having a clinically significant benefit from treatment. Similarly, treatment of a high cholesterol level with statin medications prevents a heart attack in only one of about 70 people. Yet I am a strong proponent of treating high cholesterol levels with statins because from the viewpoint of population health, it is one of the most effective things we can do to help people live longer and healthier lives.

When we move from treatment to prevention, the numbers of people who must be screened in order to produce a benefit are staggering. Screening for colon cancer is one of the most important screening tests we can do in America, yet as many as 1,500 people must undergo colonoscopy to stop one person from dying of colon cancer. For mammography, that ratio rises to a conservative number of 2,300 women who must be screened to prevent one death from breast cancer, with some data suggesting that the ratio is closer to 5,000 to 1. We should keep these numbers in mind in considering the evidence for breastfeeding.

I did some back of the envelope calculations about the number needed to breastfeed to avoid a couple of specific conditions. I freely admit that skilled biostatisticians and my colleagues at AHRQ would have concerns about my methods, and I ask you not to take these numbers as exact truths. I think they are good enough, however, to get us in the right ballpark and give us some perspective on the health benefits of breastfeeding.

Citation:
Meyers, David. "Breastfeeding and Health Outcomes." Breastfeeding Medicine 4.S1 (2009) 5.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998971/

To prevent one case of acute otitis media in an infant less than 6 months of age, approximately six children would need to be exclusively breastfed for the first 6 months. To prevent one case of vomiting and diarrhea, the number needing to breastfeed is 2.5.

Clearly, decisions about infant feeding are influenced by more than the potential health benefits for the infant. It is good to know, however, that when compared to other common treatments and preventive health choices we make, breastfeeding is very impressive. And, of course, the act of breastfeeding provides all of these benefits, not simply protection for ear infections or reducing the chances of having diabetes or preventing SIDS or preventing asthma. We need to remind ourselves not to fall into the reductionist trap when considering the health effects of breastfeeding. Breastfeeding optimizes a child's chances of reaching his or her full potential.

The review of evidence in preparing the EPC's 2007 report did not focus on children born prematurely, but on full-term infants. However, it did find a 5% absolute risk reduction for necrotizing enterocolitis among premature infants who received breastmilk.

Looking more deeply into the report, it also showed an inverse association between breastfeeding and the incidences of asthma and type 1 diabetes, but added that more evidence was needed to be conclusive about this. The report also concluded that the available evidence suggests that breastfeeding is not associated with cognitive development in full-term infants and children, although this is a very difficult area because differences in cognition can be relatively subtle, and huge numbers of children would need to be followed to find small but important effects.

Turning to the other side of the breastfeeding partnership, health benefits accrue to the mother as well as to the infant. Clear evidence was found for an inverse association of breastfeeding with breast cancer, and a strong inverse association was also found for breastfeeding and both ovarian cancer and type 2 diabetes, exclusive of gestational diabetes during pregnancy.

Although I have not had time to completely update the 2007 report for the 1,200 studies that have come out since it was published, a study that was reported in the July 2009

issue of the Journal of Obstetrics and Gynecology and that applied multivariate modeling to a large data set obtained from American women found that women who breastfed for 12 or more months across their lifetimes had lower rates of high blood pressure, hypercholesterolemia, diabetes, and known cardiovascular disease than did women who didn't breastfeed. More data and evidence are needed about this and other maternal outcomes of breastfeeding.

The team of investigators at the EPC who prepared the 2007 report had no preconceived ideas about the effects of breastfeeding. They were not advocates for or against either breastfeeding or formula feeding, and in my opinion they were conservative in their methods and their conclusions in the body of the report and a bit liberal in their writing of the executive summary.

What does the evidence say about exclusive breastfeeding? Because of changes in the way clinical studies have been done, we are getting better definitions of breastfeeding and more identification of exclusive breastfeeding as opposed to partial breastfeeding and formula feeding. And, in general, exclusive breastfeeding has produced better health outcomes than mixed feeding, which in turn has produced better health outcomes than formula feeding. When such data have been available, the benefits appear to keep increasing past 1 year of age and into the 18-month range.

On the basis of the 2007 EPC report, the U.S. Preventive Services Task Force conducted a second systematic review of the evidence about breastfeeding promotion and support in developed countries. It concluded that the actions of the healthcare system in relation to breastfeeding do matter. The Task Force recommends primary care clinicians get involved and support women in breastfeeding. It concluded that what physicians and the health system do before and around the time of delivery makes a difference in the initiation, exclusivity, and duration of breastfeeding. It also matters what we do when women and their infants leave the formal healthcare system after birth and return to the community."

Citation:
Meyers, David. "Breastfeeding and Health Outcomes." Breastfeeding Medicine 4.S1 (2009) 5.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2998971/

Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis

Abstract

CONTEXT:
Benefits of breastfeeding include lower risk of postneonatal mortality. However, it is unclear whether breastfeeding specifically lowers sudden infant death syndrome (SIDS) risk, because study results have been conflicting.

OBJECTIVE:
To perform a meta-analysis to measure the association between breastfeeding and SIDS.

METHODS:
We identified 288 studies with data on breastfeeding and SIDS through a Medline search (1966– 2009), review articles, and meta-analyses. Twenty-four original case-control studies were identified that provided data on the relationship between breastfeeding and SIDS risk. Two teams of 2 reviewers evaluated study quality according to preset criteria; 6 studies were excluded, which resulted in 18 studies for analysis. Univariable and multivariable odds ratios were extracted. A summary odds ratio (SOR) was calculated for the odds ratios by using the fixed- effect and random-effect inverse-variance methods of meta-analysis. The Breslow-Day test for heterogeneity was performed.

RESULTS:
For infants who received any amount of breast milk for any duration, the univariable SOR was 0.40 (95% confidence interval [CI]: 0.35–0.44), and the multivariable SOR was 0.55 (95% CI: 0.44–0.69). For any breastfeeding at 2 months of age or older, the univariable SOR was 0.38 (95% CI: 0.27–0.54). The univariable SOR for exclusive breastfeeding of any duration was 0.27 (95% CI: 0.24–0.31).

CONCLUSIONS:
Breastfeeding is protective against SIDS, and this effect is stronger when breastfeeding is exclusive. The recommendation to breastfeed infants should be included with other SIDS risk-reduction messages to both reduce the risk of SIDS and promote breastfeeding for its many other infant and maternal health benefits.

Citation:
Vennemann, M., J. Thompson, K. Tanabe, R. Moon, and F. Hauck. "Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis." Das Gesundheitswesen Gesundheitswesen 72.08/09 (2010)
http://pediatrics.aappublications.org/content/early/2011/06/08/peds.2010-3000

Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-risk Infants

Abstract

The purpose of this brief communication is to highlight emerging evidence to existing guidelines regarding potential benefits of supporting early, rather than delayed, peanut introduction during the period of complementary food introduction in infants. This document should be considered as interim guidance based on consensus among the following organizations: American Academy of Allergy, Asthma & Immunology, American Academy of Pediatrics, American College of Allergy, Asthma & Immunology, Australasian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society for Allergology, Society for Pediatric Dermatology, and World Allergy Organization. More formal guidelines regarding early-life, complementary feeding practices and the risk of allergy development will follow in the next year from the National Institute of Allergy and Infectious Diseases-sponsored Working Group and the European Academy of Allergy and Clinical Immunology.

Citation:
Fleischer, David M., Scott Sicherer, Matthew Greenhawt, Dianne Campbell, Edmond S. Chan, Antonella Muraro, Susanne Halken, Yitzhak Katz, Motohiro Ebisawa, Lawrence Eichenfield, and Hugh Sampson. "Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-risk Infants." World Allergy Organ J World Allergy Organization Journal 8.1 (2015) http://www.ncbi.nlm.nih.gov/pubmed/26122934.

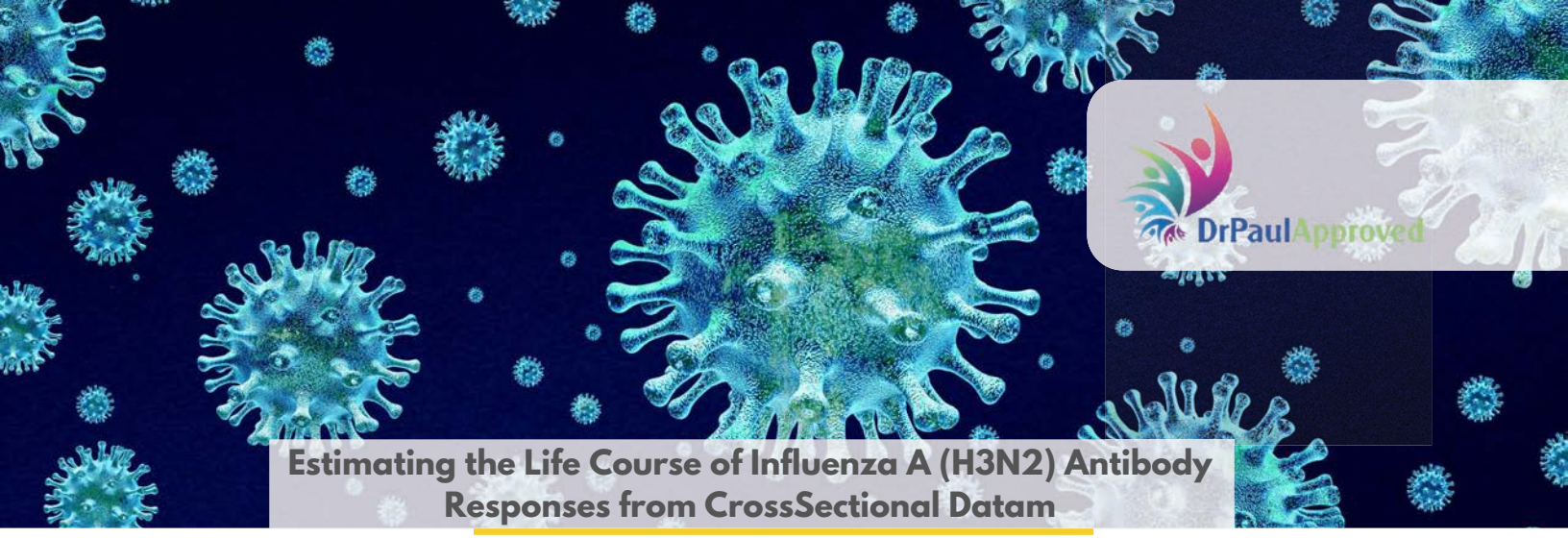
DrPaulApproved

Early Diet Impacts Infant Rhesus Gut Microbiome, Immunity, and Metabolism

Abstract

Epidemiological research has indicated a relationship between infant formula feeding and increased risk of chronic diseases later in life including obesity, type-2 diabetes, and cardiovascular disease. The present study used an infant rhesus monkey model to compare the comprehensive metabolic implications of formula- and breast-feeding practices using NMR spectroscopy to characterize metabolite fingerprints from urine and serum, in combination with anthropometric measurements, fecal microbial profiling, and cytokine measurements. Here we show that formula-fed infants are larger than their breast-fed counterparts and have a different gut microbiome that includes higher levels of bacteria from the Ruminococcus genus and lower levels of bacteria from the Lactobacillus genus. In addition, formula-fed infants have higher serum insulin coupled with higher amino acid levels, while amino acid degradation products were higher in breast-fed infants. Increases in serum and urine galactose and urine galactitol were observed in the second month of life in formula-fed infants, along with higher levels of TNFα, IFN-γ, IL-1β, IL-4, and other cytokines and growth factors at week 4. These results demonstrate that metabolic and gut microbiome development of formula-fed infants is different from breast-fed infants and that the choice of infant feeding may hold future health consequences.

Citation:
O'Sullivan, Aifric, Xuan He, Elizabeth M. S. Mcniven, Neill W. Haggarty, Bo Lönnerdal, and Carolyn M. Slupsky. "Early Diet Impacts Infant Rhesus Gut Microbiome, Immunity, and Metabolism." J. Proteome Res. Journal of Proteome Research 12.6 (2013): 2833-845.
http://pubs.acs.org/doi/abs/10.1021/pr4001702



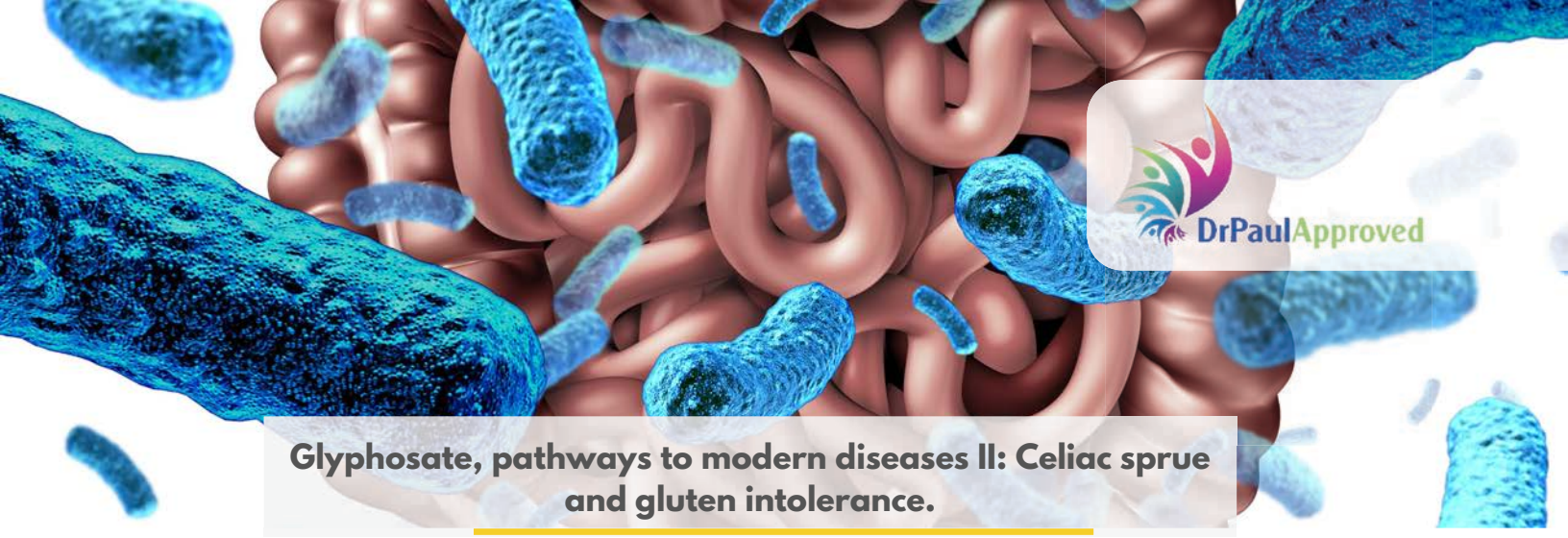
Estimating the Life Course of Influenza A (H3N2) Antibody Responses from CrossSectional Datam

Abstract

The immunity of a host population against specific influenza A strains can influence a number of important biological processes, from the emergence of new virus strains to the effectiveness of vaccination programmes. However, the development of an individual's long-lived antibody response to influenza A over the course of a lifetime remains poorly understood. Accurately describing this immunological process requires a fundamental understanding of how the mechanisms of boosting and cross-reactivity respond to repeated infections. Establishing the contribution of such mechanisms to antibody titres remains challenging because the aggregate effect of immune responses over a lifetime are rarely observed directly. To uncover the aggregate effect of multiple influenza infections, we developed a mechanistic model capturing both past infections and subsequent antibody responses. We estimated parameters of the model using cross-sectional antibody titres to nine different strains spanning 40 years of circulation of influenza A(H3N2) in southern China. We found that "antigenic seniority" and quickly decaying cross-reactivity were important components of the immune response, suggesting that the order in which individuals were infected with influenza strains shaped observed neutralisation titres to a particular virus. We also obtained estimates of the frequency and age distribution of influenza infection, which indicate

that although infections became less frequent as individuals progressed through childhood and young adulthood, they occurred at similar rates for individuals above age 30 y. By establishing what are likely to be important mechanisms driving epochal trends in population immunity, we also identified key directions for future studies. In particular, our results highlight the need for longitudinal samples that are tested against multiple historical strains. This could lead to a better understanding of how, over the course of a lifetime, fast, transient antibody dynamics combine with the longer-term immune responses considered here.

Citation:
Kucharski, Adam J., Justin Lessler, Jonathan M. Read, Huachen Zhu, Chao Qiang Jiang, Yi Guan, Derek A. T. Cummings, and Steven Riley. "Estimating the Life Course of Influenza A(H3N2) Antibody Responses from Cross-Sectional Data." PLOS Biology PLoS Biol 13.3 (2015) http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002082

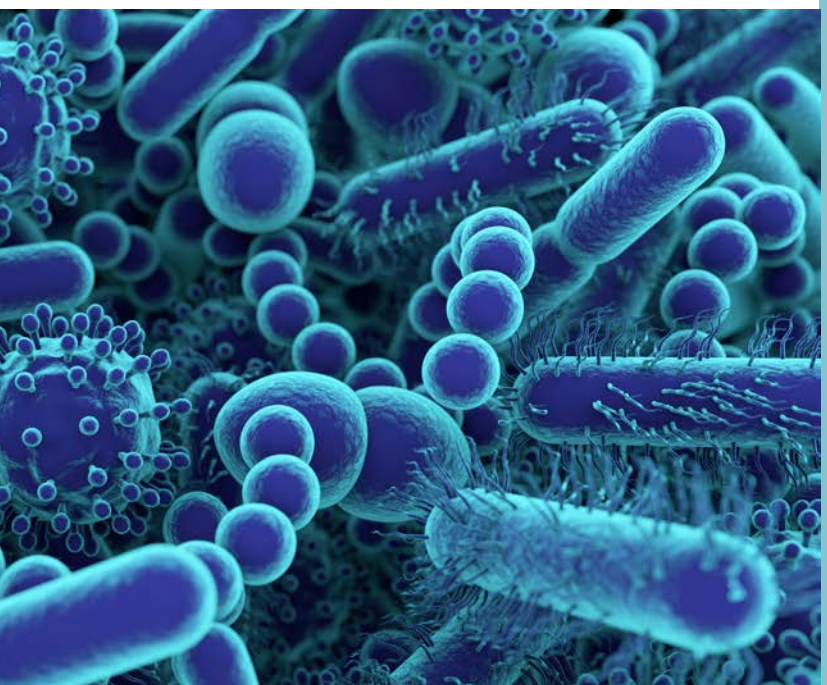


Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance.

Abstract

Celiac disease, and, more generally, gluten intolerance, is a growing problem worldwide, but especially in North America and Europe, where an estimated 5% of the population now suffers from it. Symptoms include nausea, diarrhea, skin rashes, macrocytic anemia and depression. It is a multifactorial disease associated with numerous nutritional deficiencies as well as reproductive issues and increased risk to thyroid disease, kidney failure and cancer. Here, we propose that glyphosate, the active ingredient in the herbicide, Roundup(®), is the most important causal factor in this epidemic. Fish exposed to glyphosate develop digestive problems that are reminiscent of celiac disease. Celiac disease is associated with imbalances in gut bacteria that can be fully explained by the known effects of glyphosate on gut bacteria.

Characteristics of celiac disease point to impairment in many cytochrome P450 enzymes, which are involved with detoxifying environmental toxins, activating vitamin D_3, catabolizing vitamin A, and maintaining bile acid production and sulfate supplies to the gut. Glyphosate is known to inhibit cytochrome P450 enzymes. Deficiencies in iron, cobalt, molybdenum, copper and other rare metals associated with celiac disease can be attributed to glyphosate's strong ability to chelate these elements. Deficiencies in tryptophan, tyrosine, methionine and selenomethionine associated with celiac disease match glyphosate's known depletion of these amino acids. Celiac disease patients have an increased risk to non-Hodgkin's lymphoma, which has also been implicated in glyphosate exposure. Reproductive issues associated with celiac disease, such as infertility, miscarriages, and birth defects, can also be explained by glyphosate. Glyphosate residues in wheat and other crops are likely increasing recently due to the growing practice of crop desiccation just prior to the harvest. We argue that the practice of "ripening" sugar cane with glyphosate may explain the recent surge in kidney failure among agricultural workers in Central America. We conclude with a plea to governments to reconsider policies regarding the safety of glyphosate residues in foods.



Citation:
Samsel, Anthony, and Stephanie Seneff. "Glyphosate, Pathways to Modern Diseases II: Celiac Sprue and Gluten Intolerance." Interdisciplinary Toxicology 6.4 (2013)
http://www.ncbi.nlm.nih.gov/pubmed/24678255

Primary prevention of allergic disease through nutritional interventions.

Abstract

With the rising prevalence of atopic disease, primary prevention may play a role in reducing its burden, especially in high-risk infants. With this in mind, the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma &Immunology was charged with the task of developing recommendations for primary care physicians and specialists about the primary prevention of allergic disease through nutritional interventions according to current available literature and expert opinion. Recommendations that are supported by data are as follows. Avoidance diets during pregnancy and lactation are not recommended at this time, but more research is necessary for peanut. Exclusive breast-feeding for at least 4 and up to 6 months is endorsed. For high-risk infants who cannot be exclusively breast-fed, hydrolyzed formula appears to offer advantages to prevent allergic disease and cow's milk allergy. Complementary foods can be introduced between 4 and 6 months of age. Because no formal recommendations have been previously provided about how and when to introduce the main allergenic foods (cow's milk, egg, soy, wheat, peanut, tree nuts, fish, shellfish), these are now provided, and reasons to consider allergy consultation for development of a personalized plan for food introduction are also presented.

Citation:
Fleischer, David M., Jonathan M. Spergel, Amal H. Assa'ad, and Jacqueline A. Pongracic. "Primary Prevention of Allergic Disease Through Nutritional Interventions." The Journal of Allergy and Clinical Immunology: In Practice 1.1 (2013): 29-36.
http://www.ncbi.nlm.nih.gov/pubmed/24229819

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

Abstract

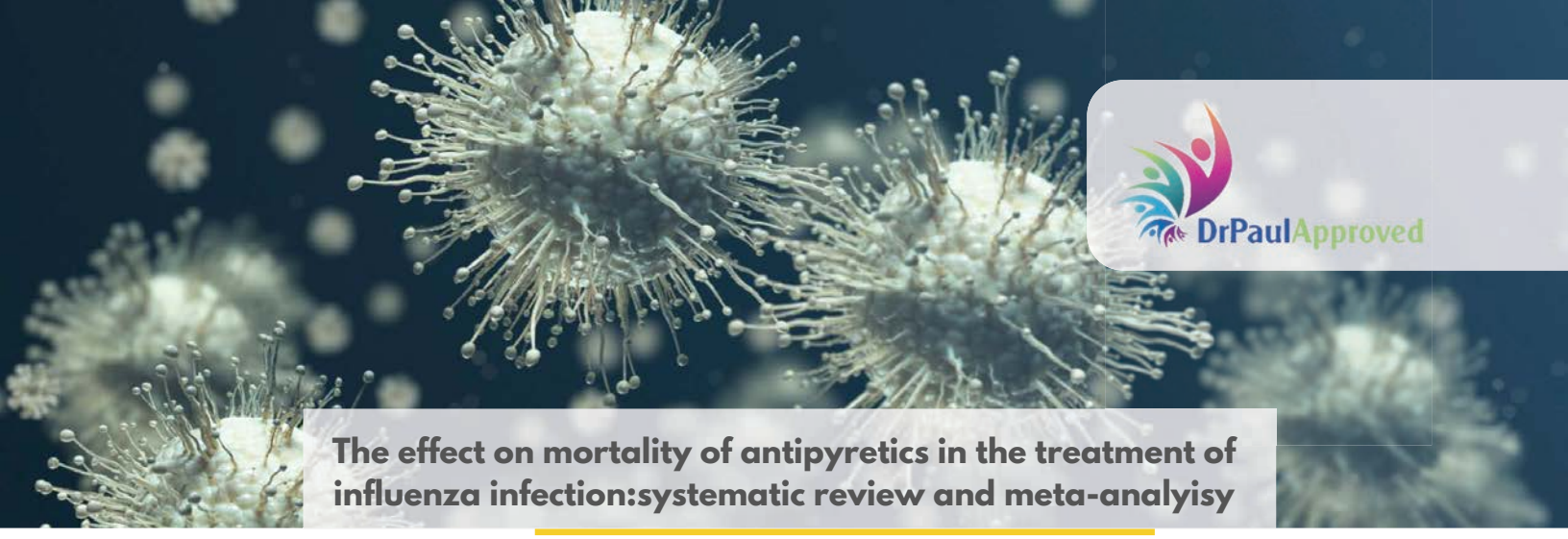
BACKGROUND:
The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

METHODS:
We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test — one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.

RESULTS:
Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group (P<0.001). Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004). There was no significant between-group difference in the incidence of serious adverse events. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

CONCLUSIONS:
The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00329784.)

Citation:
Chipps, B. E. "Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy." Pediatrics 136.Supplement (2015)
http://www.nejm.org/doi/full/10.1056/NEJMoa1414850#t=article



The effect on mortality of antipyretics in the treatment of influenza infection:systematic review and meta-analyisy

Abstract

To determine whether antipyretic treatment for influenza infection influences the risk of mortality in animal models and humans.

DESIGN:
A systematic search of Medline, Embase and the Cochrane Register of Controlled Trials was undertaken to identify randomized placebo-controlled trials of antipyretic use in influenza infection in animal models or humans that reported mortality. A quantitative meta-analysis of the risk of death using Peto's one step odds ratio with calculation of the pooled risk of death and standard evaluation of heterogeneity was undertaken.

SETTING:
Not applicable.

PARTICIPANTS:
Not applicable.

MAIN OUTCOME MEASURES:
Risk of mortality associated with antipyretic use in influenza infection.

RESULTS:
Eight studies from three publications met the inclusion criteria. No human studies were identified. The risk of mortality was increased by antipyretic use in influenza-infected animals with a fixed effects pooled odds ratio of 1.34 (95% CI 1.04-1.73). An increased risk was observed with aspirin, paracetamol and diclofenac.

CONCLUSION:
In animal models, treatment with antipyretics for influenza infection increases the risk of mortality. There are no randomized placebo-controlled trials of antipyretic use in influenza infection in humans that reported data on mortality and a paucity of clinical data by which to assess their efficacy. We suggest that randomized placebo-controlled trials of antipyretic use in human influenza infection are urgently required, and that these are sufficiently powered to investigate a potential effect on mortality.

Citation:
Eyers, S., M. Weatherall, P. Shirtcliffe, K. Perrin, and R. Beasley. "The Effect on Mortality of Antipyretics in the Treatment of Influenza Infection: Systematic Review and Meta- analyis." Jrsm 103.10 (2010): 403-11.
http://www.ncbi.nlm.nih.gov/pubmed/20929891

DrPaulApproved

There is (still) too much aluminium in infant formulas

Abstract

To determine whether antipyretic treatment for influenza infection influences the risk of mortality in animal models and humans.

BACKGROUND:
Infant formulas are sophisticated milk-based feeds for infants which are used as a substitute for breast milk. Historically they are known to be contaminated by aluminium and in the past this has raised health concerns for exposed infants. We have measured the aluminium content of a number of widely used infant formulas to determine if their contamination by aluminium and consequent issues of child health persists.

METHODS:
Samples of ready-made milks and powders used to make milks were prepared by microwave digestion of acid/peroxide mixtures and their aluminium content determined by THGA.

RESULTS:
The concentration of aluminium in ready-made milks varied from ca 176 to 700 μg/L. The latter concentration was for a milk for preterm infants. The aluminium content of powders used to make milks varied from ca 2.4 to 4.3 μg/g. The latter content was for a soya-based formula and equated to a ready-to-drink milk concentration of 629 μg/L. Using the manufacturer's own guidelines of formula consumption the average daily ingestion of aluminium from infant formulas for a child of 6 months varied from ca 200 to 600 μg of aluminium. Generally ingestion was higher from powdered as compared to ready-made formulas.

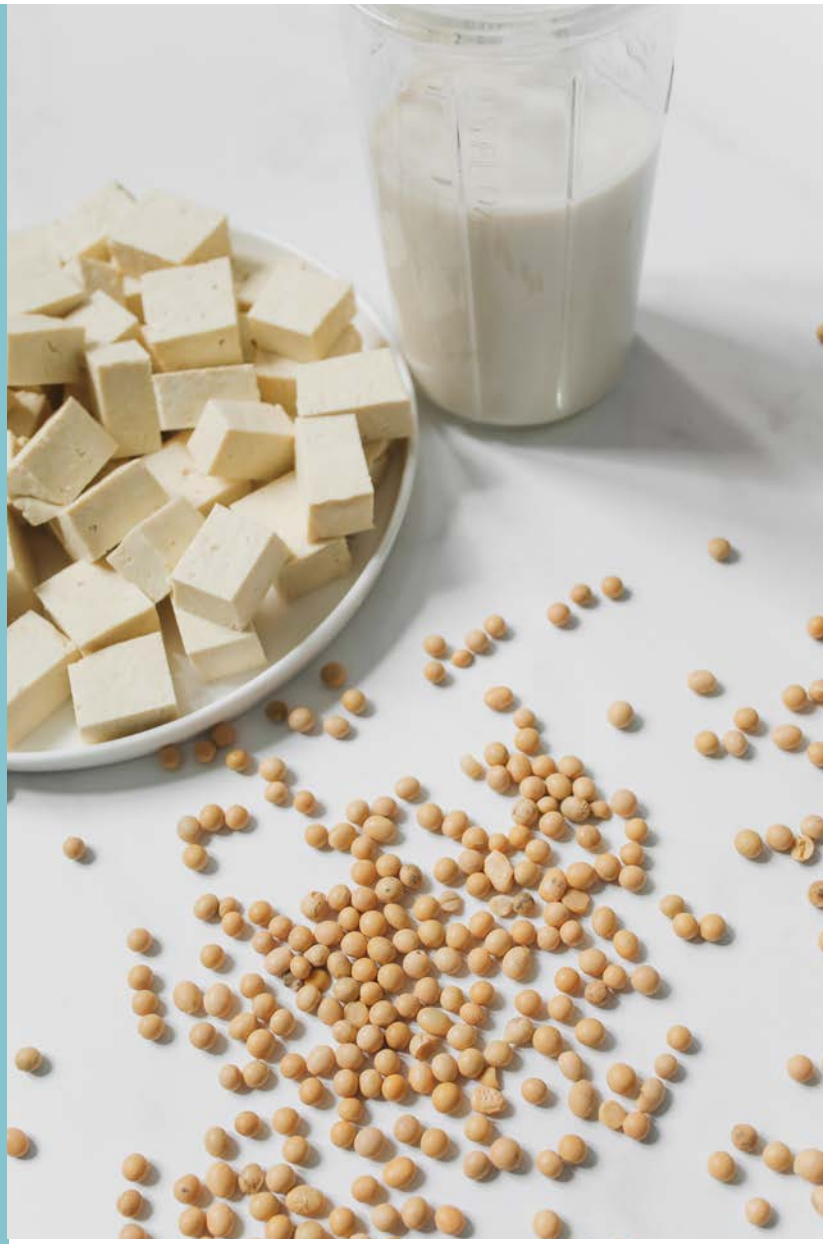
CONCLUSIONS:
The aluminium content of a range of well known brands of infant formulas remains high and particularly so for a product designed for preterm infants and a soya-based product designed for infants with cow's milk intolerances and allergies. Recent research demonstrating the vulnerability of infants to early exposure to aluminium serves to highlight an urgent need to reduce the aluminium content of infant formulas to as low a level as is practically possible.

Citation:
Burrell, Shelle-Ann M., and Christopher Exley. "There Is (still) Too Much Aluminium in Infant Formulas." BMC Pediatrics BMC Pediatr 10.1 (2010) http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-10-63

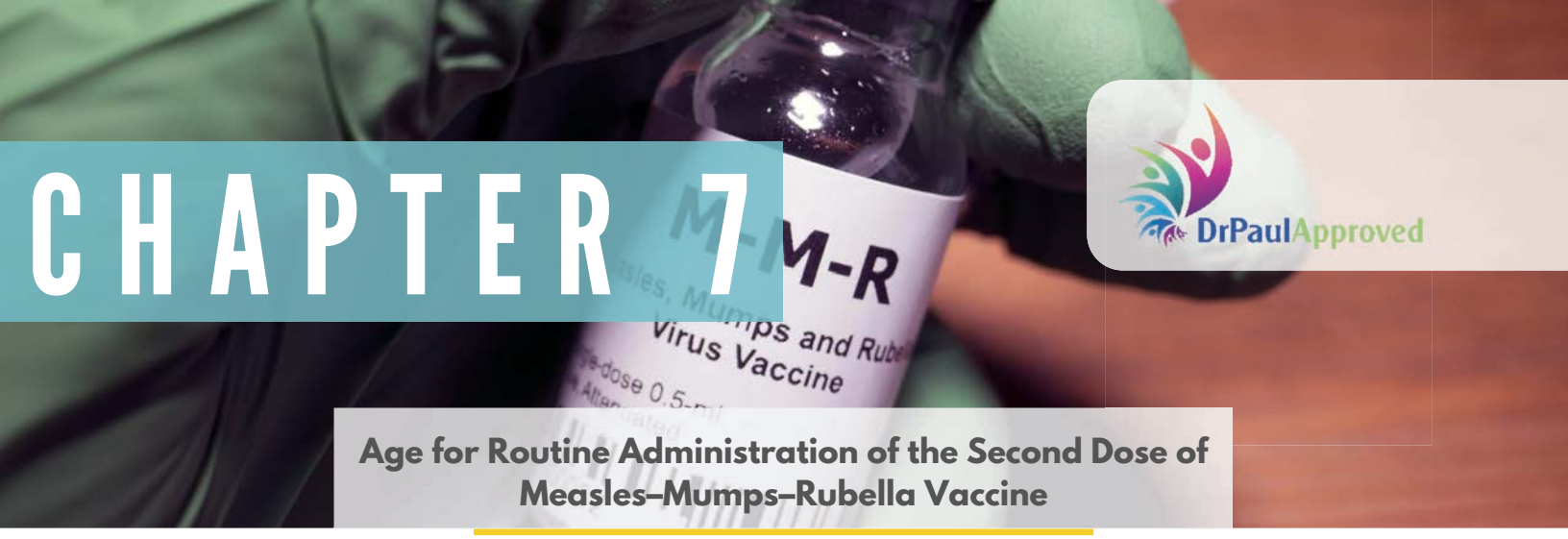
Use of Soy Protein-Based Formulas in Infant Feeding

Abstract

Soy protein-based formulas have been available for almost 100 years. Since the first use of soy formula as a milk substitute for an infant unable to tolerate a cow milk protein-based formula, the formulation has changed to the current soy protein isolate. Despite very limited indications for its use, soy protein-based formulas in the United States may account for nearly 25% of the formula market. This report reviews the limited indications and contraindications of soy formulas. It will also review the potential harmful effects of soy protein-based formulas and the phytoestrogens contained in these formulas.



Citation:
Bhatia, J., and F. Greer. "Use of Soy Protein-Based Formulas in Infant Feeding." Pediatrics 121.5 (2008): 1062-068.
http://pediatrics.aappublications.org/content/121/5/1062

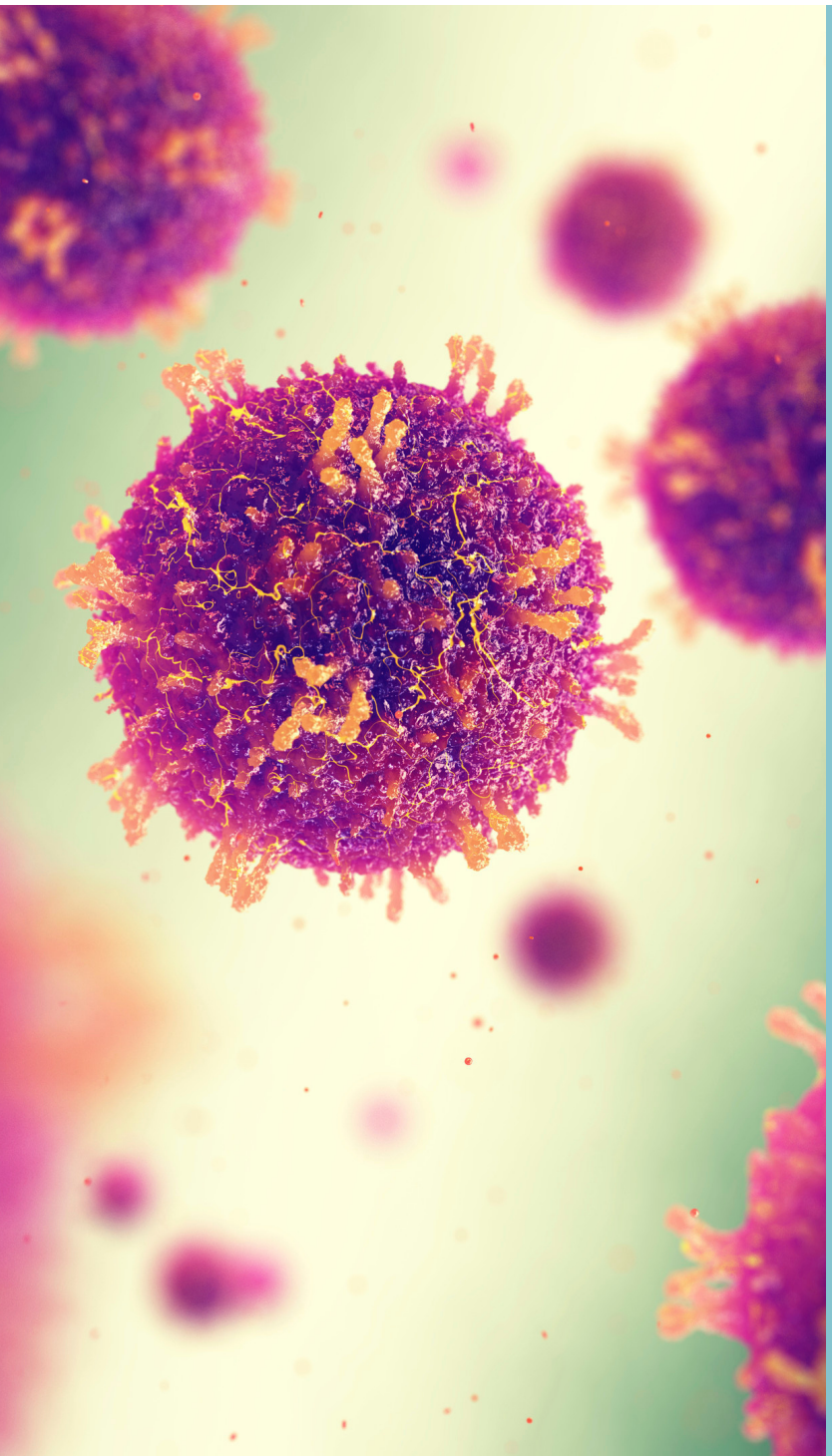


CHAPTER 7

DrPaulApproved

Age for Routine Administration of the Second Dose of Measles–Mumps–Rubella Vaccine

Abstract



The purpose of this statement is to inform physicians of a modification in the recommendation of the appropriate age for routine administration of the second dose of measles–mumps–rubella (MMR) vaccine. The implementation of the two-dose measles vaccine schedule has improved the control of measles, but some outbreaks continue to occur in school children, although <95% of children in school have received one dose of vaccine. Because most measles vaccine failures are attributable to failure to respond to the first dose, that all children receive two doses of measles-containing vaccine is essential for the control of measles. Routine administration of the second dose of MMR vaccine at school entry (4 to 6 years of age) will help prevent schoolbased outbreaks. Physicians should continue to review the records of all children 11 to 12 years of age to be certain that they have received two doses of MMR vaccine after their first birthday. Documenting that all school children have received two doses of measles-containing vaccine by the year 2001 will help ensure the elimination of measles in the United States and contribute to the global effort to control and possibly eradicate measles.

Citation:
"Age for Routine Administration of the Second Dose of Measles-Mumps-Rubella Vaccine." Pediatrics 101.1 (1998): 129-33.
http://pediatrics.aappublications.org/content/101/1/129

Can Awareness of Medical Pathophysiology in Autism Lead to Primary Care Autism Prevention Strategies?

Abstract

Emerging research suggests that the timing of environmental factors in the presence of genetic predispositions has influenced the increase in autism spectrum disorders over the past several decades. A review of the medical literature suggests that autism may be impacted by environmental toxicants, breastfeeding duration, gut flora composition, nutritional status, acetaminophen use, vaccine practices and use of antibiotics and/or frequency of infections. The author reports her retrospective clinical research in a general pediatric practice (Advocates for Children), which shows a modest trend toward lower prevalence of autism than her previous pediatric practice or recent CDC data. Out of 294 general pediatrics patients followed since 2005 there were zero new cases of autism (p value 0.014). Given the prevalence of autism for that cohort of 1 in 50 children in the United States, it is important to consider implementing strategies in primary care practice that could potentially modify environmental factors or affect the timing of environmental triggers contributing to autism.

Citation:
Elizabeth Mumper." Can Awareness of Medical Pathophysiology in Autism Lead to Primary CareAutism Prevention Strategies?". North American Journal of Medicine and Science. Jul 2013 Vol 6 No.3
http://www.ncbhttp://www.tocureautism.org/our-publications/2013/2013-6i.nlm.nih.gov/pubmed/24521589

DrPaulApproved

Measles-mumps-rubella vaccination timing and autism among young african american boys: a reanalysis of CDC data

Abstract

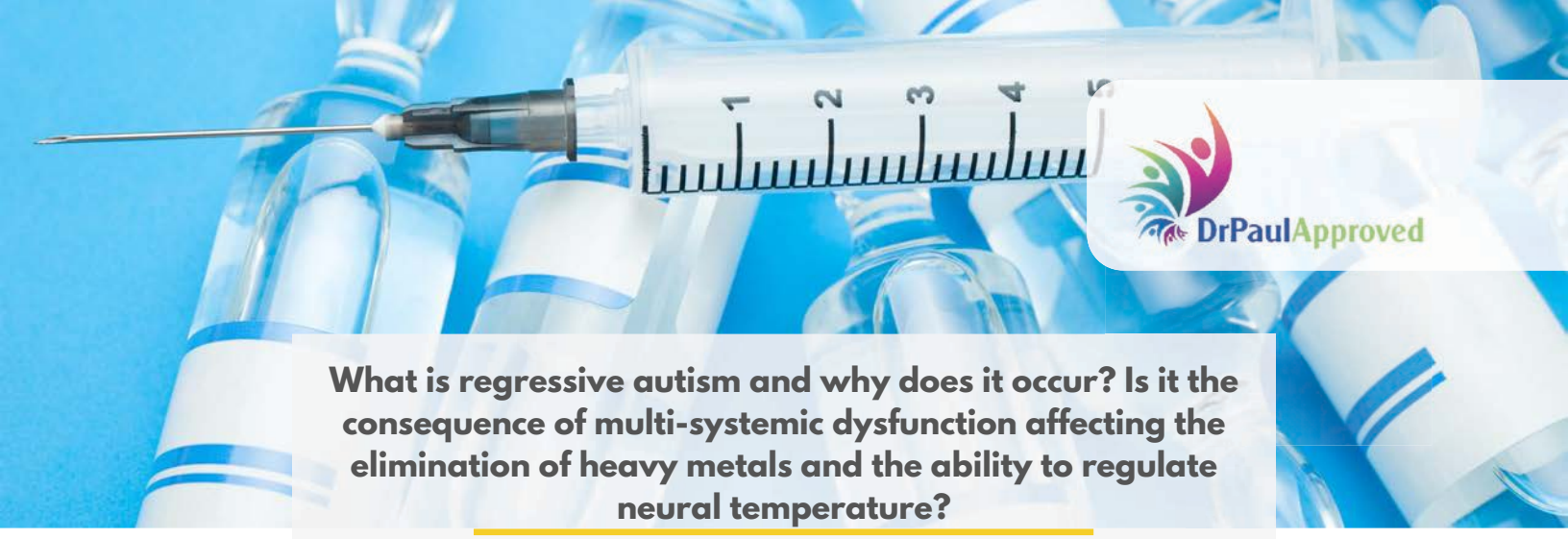
BACKGROUND:
A significant number of children diagnosed with autism spectrum disorder suffer a loss of previously-acquired skills, suggesting neurodegeneration or a type of progressive encephalopathy with an etiological basis occurring after birth. The purpose of this study is to investigate the effectof the age at which children got their first Measles-Mumps-Rubella (MMR) vaccine on autism incidence. This is a reanalysis of the data set, obtained from the U.S. Centers for Disease Control and Protection (CDC), used for the Destefano et al. 2004 publication on the timing of the first MMR vaccine and autism diagnoses.

METHODS:
The author embarked on the present study to evaluate whether a relationship exists between child age when the first MMR vaccine was administered among cases diagnosed with autism and controls born between 1986 through 1993 among school children in metropolitan Atlanta. The Pearson's chi-squared method was used to assess relative risks of receiving an autism diagnosis within the total cohort as well as among different race and gender categories.

RESULTS:
When comparing cases and controls receiving their first MMR vaccine before and after 36 months of age, there was a statistically significant increase in autism cases specifically among African American males who received the first MMR prior to 36 months of age. Relative risks for males in general and African American males were 1.69 (p=0.0138) and 3.36 (p=0.0019), respectively. Additionally, African American males showed an odds ratio of 1.73 (p=0.0200) for autism cases in children receiving their first MMR vaccine prior to 24 months of age versus 24 months of age and thereafter.

CONCLUSION:
The present study provides new epidemiologic evidence showing that African American males receiving the MMR vaccine prior to 24 months of age or 36 months of age are more likely to receive an autism diagnosis.

Citation:
Hooker, Brian S. "Measles-mumps-rubella Vaccination Timing and Autism among Young African American Boys: A Reanalysis of CDC Data." Transl Neurodegener Translational Neurodegeneration 3.1 (2014): 16.
https://translationalneurodegeneration.biomedcentral.com/articles/10.1186/2047-9158-3-16



DrPaulApproved

What is regressive autism and why does it occur? Is it the consequence of multi-systemic dysfunction affecting the elimination of heavy metals and the ability to regulate neural temperature?

Abstract

There is a compelling argument that the occurrence of regressive autism is attributable to genetic and chromosomal abnormalities, arising from the overuse of vaccines, which subsequently affects the stability and function of the autonomic nervous system and physiological systems. That sense perception is linked to the autonomic nervous system and the function of the physiological systems enables us to examine the significance of autistic symptoms from a systemic perspective. Failure of the excretory system influences elimination of heavy metals and facilitates their accumulation and subsequent manifestation as neurotoxins: the long-term consequences of which would lead to neurodegeneration, cognitive and developmental problems. It may also influence regulation of neural hyperthermia. This article explores the issues and concludes that sensory dysfunction and systemic failure, manifested as autism, is the inevitable consequence arising from subtle DNA alteration and consequently from the overuse of vaccines.

Citation:
Ewing GE. What is regressive autism and why does it occur? Is it the consequence of multi- systemic dysfunction affecting the elimination of heavy metals and the ability to regulate neural temperature? North American Journal of Medical Sciences. 2009;1(2):28-47.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364648/

CHAPTER 8

DrPaulApproved

Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan atlanta

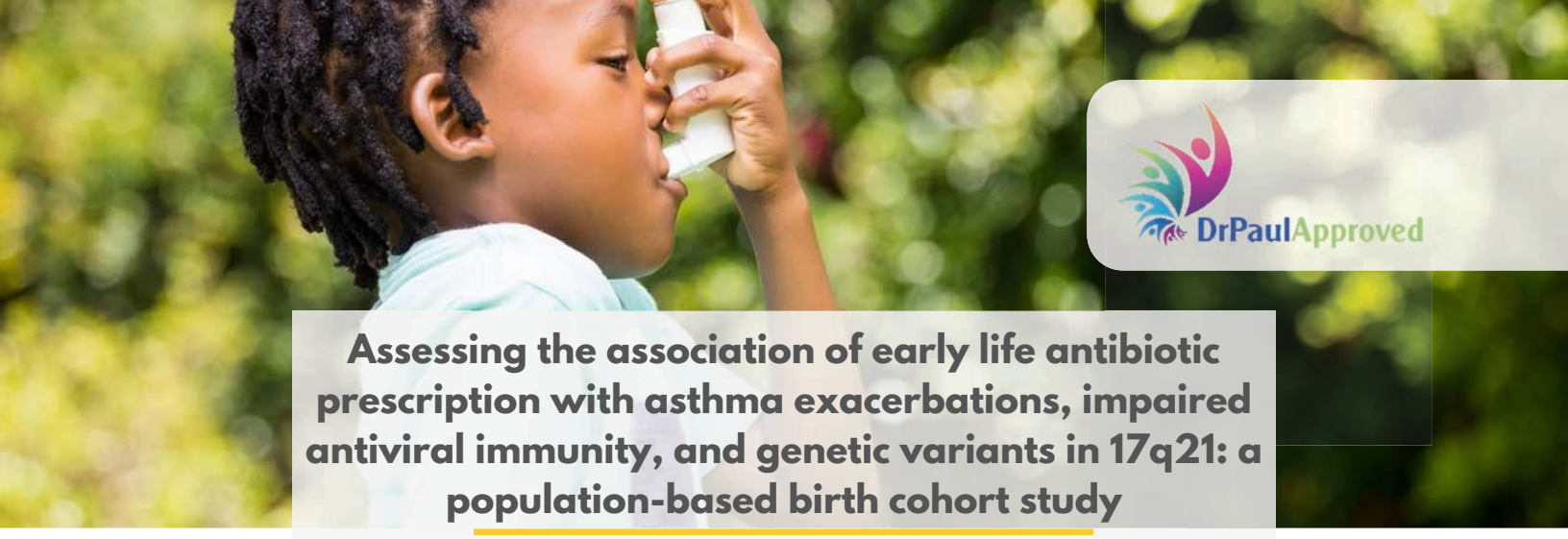
Abstract

OBJECTIVES:
To compare ages at first measles-mumps-rubella (MMR) vaccination between children with autism and children who did not have autism in the total population and in selected subgroups, including children with regression in development. A case-control study was conducted in metropolitan Atlanta. Case children (N = 624) were identified from multiple sources and matched to control children (N = 1824) on age, gender, and school. Vaccination data were abstracted from immunization forms required for school entry. Records of children who were born in Georgia were linked to Georgia birth certificates for information on maternal and birth factors. Conditional logistic regression was used to estimate odds ratios (ORs).

RESULTS:
The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children; most case (70.5%) and control children (67.5%) were vaccinated between 12 and 17 months of age. Similar proportions of case and control children had been vaccinated before 18 or before 24 months. No significant associations for either of these age cutoffs were found for specific case subgroups, including those with evidence of developmental regression. More case (93.4%) than control children (90.6%) were vaccinated before 36 months (OR: 1.49; 95% confidence interval: 1.04-2.14 in the total sample; OR: 1.23; 95% confidence interval: 0.64-2.36 in the birth certificate sample). This association was strongest in the 3- to 5-year age group.

CONCLUSIONS:
Similar proportions of case and control children were vaccinated by the recommended age or shortly after (ie, before 18 months) and before the age by which atypical development is usually recognized in children with autism (ie, 24 months). Vaccination before 36 months was more common among case children than control children, especially among children 3 to 5 years of age, likely reflecting immunization requirements for enrollment in early intervention programs.

Citation:
Destefano, F., T. K. Bhasin, W. W. Thompson, M. Yeargin-Allsopp, and C. Boyle. "Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta." Pediatrics 113.2 (2004): 259-66.
http://www.ncbi.nlm.nih.gov/pubmed/14754936



Assessing the association of early life antibiotic prescription with asthma exacerbations, impaired antiviral immunity, and genetic variants in 17q21: a population-based birth cohort study

Abstract

BACKGROUND:

The relationship between early-life antibiotic use and the development of wheeze and asthma has been reported in several studies but might arise as a consequence of bias rather than causal relationship. We investigated the association between antibiotic
prescription and subsequent development of atopy, wheeze, and asthma exacerbations, and the relation of early life antibiotic prescription with anti-infective immunity and genetic variants on asthma susceptibility locus 17q21.

METHODS:

Children in a population-based birth cohort were followed from birth to age 11 years. Information on antibiotic prescription, wheeze, and asthma exacerbations was extracted from medical records, and the effect of antibiotic prescription assessed with longitudinal analyses. We assessed immune responses of peripheral blood mononuclear cells, taken at age 11 years, to viruses (rhinovirus and respiratory syncytial virus; RSV) and bacteria (Haemophilus influenzae and Streptococcus pneumoniae) in children who either received at least one or no antibiotic prescriptions in infancy. Finally, we assessed the association of 17q21 polymorphisms with antibiotic prescription.

FINDINGS:

Of 984 families who gave consent, we extracted data for 916 children. We noted significantly higher risk of physician-confirmed wheezing after antibiotic prescription (hazard ratio [HR] 1·71, 95% CI 1·32–2·23; p<0·0001) and severe wheeze or asthma
exacerbation after antibiotic prescription (HR 2·26, 95% CI 1·03–4·94; p=0·041). In children who wheezed, the hazards of exacerbations (2·09, 1·51–2·90; p<0·0001) and admissions to hospital (2·64, 1·49–4·70; p=0·0009) were significantly increased in the 2 years after the first antibiotic prescription. Children who received antibiotics in infancy had significantly lower induction of cytokines, which are important in host defence against virus infections to both RSV and rhinovirus; there were no differences in antibacterial responses. Variants in 17q21 were associated with an increased risk of early life antibiotic prescription.

INTERPRETATION:

The association between antibiotics and asthma might arise through a complex confounding by indication. Hidden factors that may increase the likelihood of both early life antibiotic prescription and later asthma are an increased susceptibility to viral infections consequent upon impaired antiviral immunity and genetic variants on 17q21.

Citation:

Semic-Jusufagic, Aida, Danielle Belgrave, Andrew Pickles, Aurica G. Telcian, Eteri Bakhsoliani, Annemarie Sykes, Angela Simpson, Sebastian L. Johnston, and Adnan Custovic. "Assessing the Association of Early Life Antibiotic Prescription with Asthma Exacerbations, Impaired Antiviral Immunity, and Genetic Variants in 17q21: A Population-based Birth Cohort Study." The Lancet Respiratory Medicine 2.8 (2014): 621-30

http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(14)70096-7/abstract

DrPaulApproved

Complementary and alternative medicine for prevention and treatment of the common cold.

Abstract

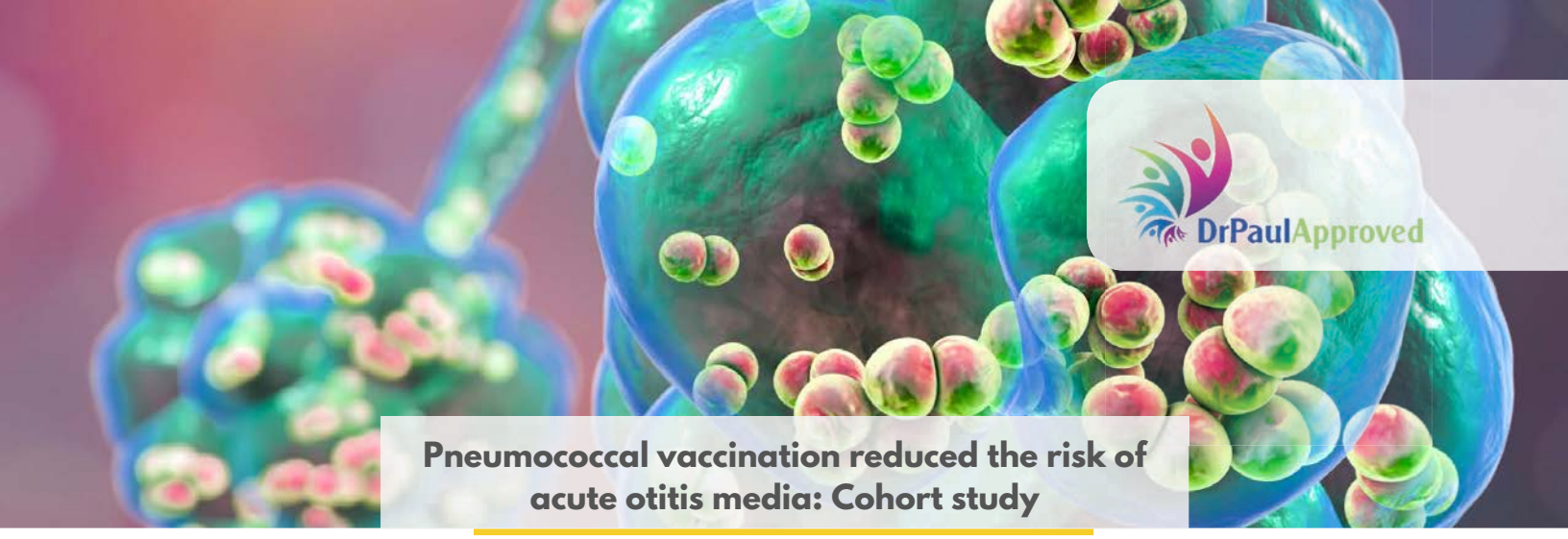
To review the evidence supporting complementary and alternative medicine approaches to treatment and prevention of the common cold in adults.

QUALITY OF EVIDENCE:
MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from January 1966 to September 2009 combining the key words common cold or influenza with echinacea, garlic, ginseng, probiotics, vitamin C, and zinc. Clinical trials and prospective studies were included.

MAIN MESSAGE:
For prevention, vitamin C demonstrated benefit in a large meta-analysis, with possibly increased benefit in patients subjected to cold stress. There is inconsistent evidence for Asian ginseng (Panax ginseng) and North American ginseng (Panax quinquefolius). Allicin was highly effective in 1 small trial. For treatment, Echinacea purpurea is the most consistently useful variety; it was effective in 5 of 6 trials. Zinc lozenges were effective in 5 of 9 trials, likely owing to dose and formulation issues. Overall, the evidence suggests no benefit from probiotics for prevention or treatment of the common cold.

CONCLUSION:
Vitamin C can be recommended to Canadian patients for prevention of the common cold. There is moderate evidence supporting the use of Echinacea purpurea and zinc lozenges for treatment. Ginseng and allicin warrant further research.

Citation:
Mousa, H. A.-L. "Prevention and Treatment of Influenza, Influenza-Like Illness, and Common Cold by Herbal, Complementary, and Natural Therapies." Journal of Evidence-Based Complementary & Alternative Medicine (2016)
https://pubmed.ncbi.nlm.nih.gov/21322286/



Pneumococcal vaccination reduced the risk of acute otitis media: Cohort study

Abstract

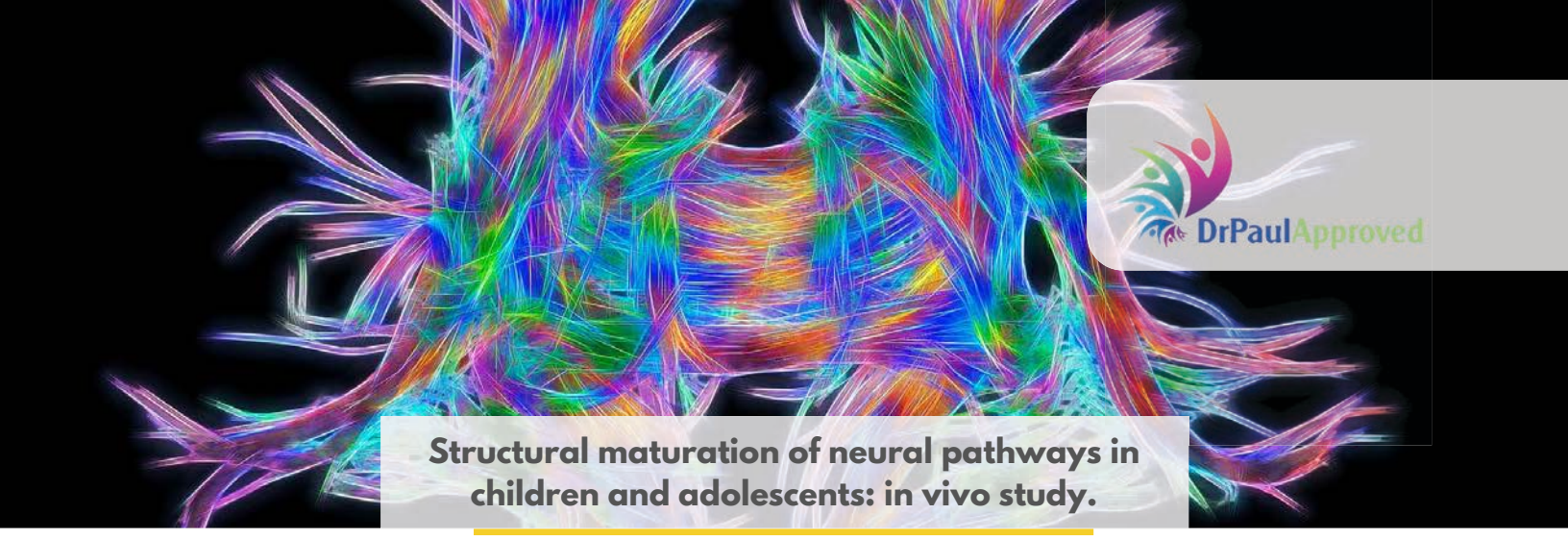
BACKGROUND:
Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced to Japan in 2009, and after that invasive pneumococcal disease has gradually decreased. There are few data, however, on the effectiveness of PCV7 against acute otitis media (AOM) in Japan.

METHODS:
From 10 daycare centers in Sapporo, Japan, 614 parents participated in the survey. Each parent reported whether their child subject had received one or more doses of PCV7, and, if so, the exact dates of receiving PCV7 were verified by reviewing their maternal and child health handbooks marked by a pediatrician. AOM was diagnosed by otorhinolaryngologist or pediatrician. Cox's proportional hazard model was used for calculating the hazard ratio (HR) of AOM incidence reduced by PCV7 inoculation.

RESULTS:
Inoculation of PCV7 significantly reduced the risk of AOM (crude HR, 0.63; 95%CI:0.50-0.79). Adjusting for potentially confounding variables reduced the risk further (adjusted HR, 0.32; 95%CI: 0.23-0.44). On stratification by subject age on 30 April 2012, PCV7 was significantly associated with a reduced risk of AOM in both infants >3 years old, and in children ⩾ 3 years.

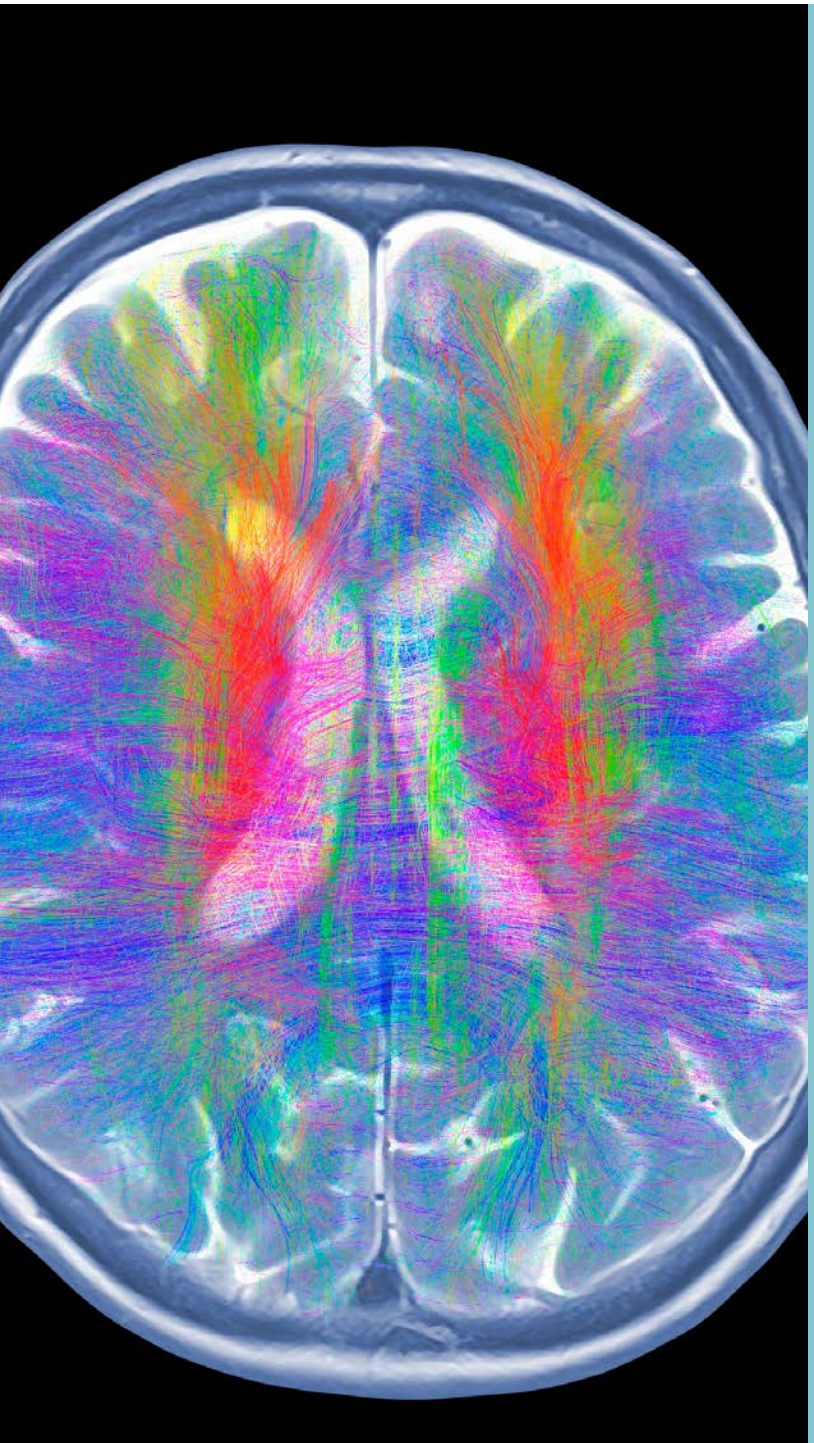
CONCLUSION:
PCV7 is effectiveness in reducing the risk of AOM both in infants >3 years old, and in young children ⩾ 3 years in Japan.

Citation:
Hasegawa, Junko, Mitsuru Mori, Satoko Showa, Aiko Matsushima, Hirofumi Ohnishi, Takeshi Tsugawa, Yuko Yoto, and Hiroyuki Tsutsumi. "Pneumococcal Vaccination Reduced the Risk of Acute Otitis Media: Cohort Study." Pediatrics International Pediatr Int 57.4 (2015): 582-85.
http://www.ncbi.nlm.nih.gov/pubmed/25615843



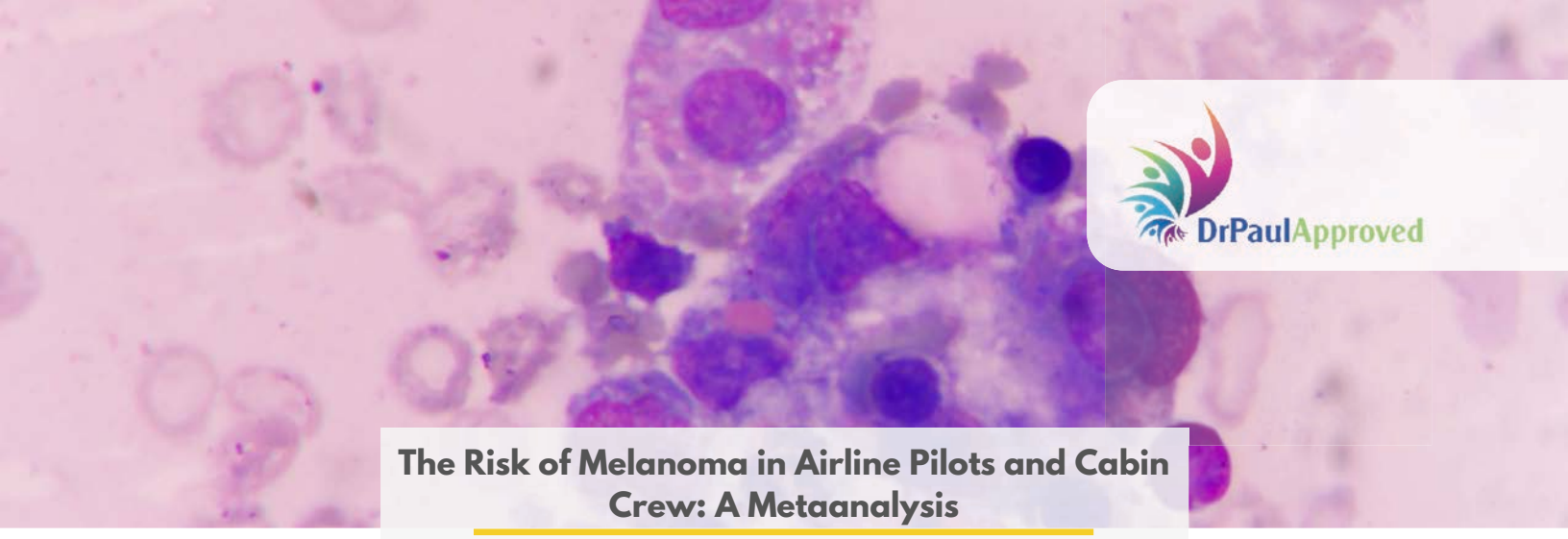
Structural maturation of neural pathways in children and adolescents: in vivo study.

Abstract



Structural maturation of fiber tracts in the human brain, including an increase in the diameter and myelination of axons, may play a role in cognitive development during childhood and adolescence. A computational analysis of structural magnetic resonance images obtained in 111 children and adolescents revealed age-related increases in white matter density in fiber tracts constituting putative corticospinal and frontotemporal pathways. The maturation of the corticospinal tract was bilateral, whereas that of the frontotemporal pathway was found predominantly in the left (speech-dominant) hemisphere. These findings provide evidence for a gradual maturation, during late childhood and adolescence, of fiber pathways presumably supporting motor and speech functions.

Citation:
Paus, T. S. A. A. "Structural Maturation of Neural Pathways in Children and Adolescents: In Vivo Study." Science 283.5409 (1999): 1908-911. http://www.ncbi.nlm.nih.gov/pubmed/10082463



The Risk of Melanoma in Airline Pilots and Cabin Crew: A Metaanalysis

Abstract

Airline pilots and cabin crew are occupationally exposed to higher levels of cosmic and UV radiation than the general population, but their risk of developing melanoma is not yet established.

OBJECTIVE:
To assess the risk of melanoma in pilots and airline crew.

DATA SOURCES:
PubMed (1966 to October 30, 2013), Web of Science (1898 to January 27, 2014), and Scopus (1823 to January 27, 2014).

STUDY SELECTION:
All studies were included that reported a standardized incidence ratio (SIR), standardized mortality ratio (SMR), or data on expected and observed cases of melanoma or death caused by melanoma that could be used to calculate an SIR or SMR in any flight-based occupation.

DATA EXTRACTION AND SYNTHESIS:
Primary random-effect meta-analyses were used to summarize SIR and SMR for melanoma in any flight-based occupation. Heterogeneity was assessed using the χ2 test and I2 statistic. To assess the potential bias of small studies, we used funnel plots, the Begg rank correlation test, and the Egger weighted linear regression test.

MAIN OUTCOMES AND MEASURES:
Summary SIR and SMR of melanoma in pilots and cabin crew.

RESULTS:
Of the 3527 citations retrieved, 19 studies were included, with more than 266 431 participants. The overall summary SIR of participants in any flight-based occupation was 2.21 (95% CI, 1.76- 2.77; P < .001; 14 records). The summary SIR for pilots was 2.22 (95% CI, 1.67-2.93; P = .001; 12 records). The summary SIR for cabin crew was 2.09 (95% CI, 1.67-2.62; P = .45; 2 records). The overall summary SMR of participants in any flight-based occupation was 1.42 (95% CI, 0.89-2.26; P = .002; 6 records). The summary SMR for pilots was 1.83 (95% CI, 1.27-2.63, P = .33; 4 records). The summary SMR for cabin crew was 0.90 (95% CI, 0.80-1.01; P = .97; 2 records).

CONCLUSIONS AND RELEVANCE:
Pilots and cabin crew have approximately twice the incidence of melanoma compared with the general population. Further research on mechanisms and optimal occupational protection is needed.

Citation:
Sanlorenzo, Martina, Mackenzie R. Wehner, Eleni Linos, John Kornak, Wolfgang Kainz, Christian Posch, Igor Vujic, Katia Johnston, Deborah Gho, Gabriela Monico, James T. Mcgrath, Simona Osella-Abate, Pietro Quaglino, James E. Cleaver, and Susana Ortiz- Urda. "The Risk of Melanoma in Airline Pilots and Cabin Crew." JAMA Dermatol JAMA Dermatology 151.1 (2015): 51.
http://www.ncbi.nlm.nih.gov/pubmed/25188246

DrPaulApproved

Zinc gluconate and the common cold: a controlled clinical study.

Abstract

A report in 1984 on the success of zinc gluconate against common cold symptoms could not be confirmed in three subsequent studies, which are now known to have used formulations that inactivated zinc. A non-chelating formulation including glycine, which releases 93% of contained zinc into saliva, was tested in a randomized, placebo-controlled, double-blind trial in 73 young adults. Efficacy was recorded in symptom diaries using a symptom severity rating. Patients' symptoms first appeared 1.34 days prior to entry to the study in both groups. Disappearance of symptoms occurred after an additional 4.9 days for zinc-treated patients versus 6.1 days for placebo-treated patients. A difference was noted in the efficacy of treatment if it was started 1 day after symptom onset: cold duration was an additional 4.3 days in zinc-treated patients compared with 9.2 days for placebo-treated patients. Cough, nasal drainage and congestion were the symptoms most affected, and only mild side-effects were noted.

Citation:
Godfrey JC , Conant Sloane B, Smith DS, Turco JH, Mercer N, Godfrey NJ." Zinc gluconate and the common cold: a controlled clinical study." J Int Med Res. 1992 Jun;20(3):234-46.
http://www.ncbi.nlm.nih.gov/pubmed/1397668

CHAPTER 9

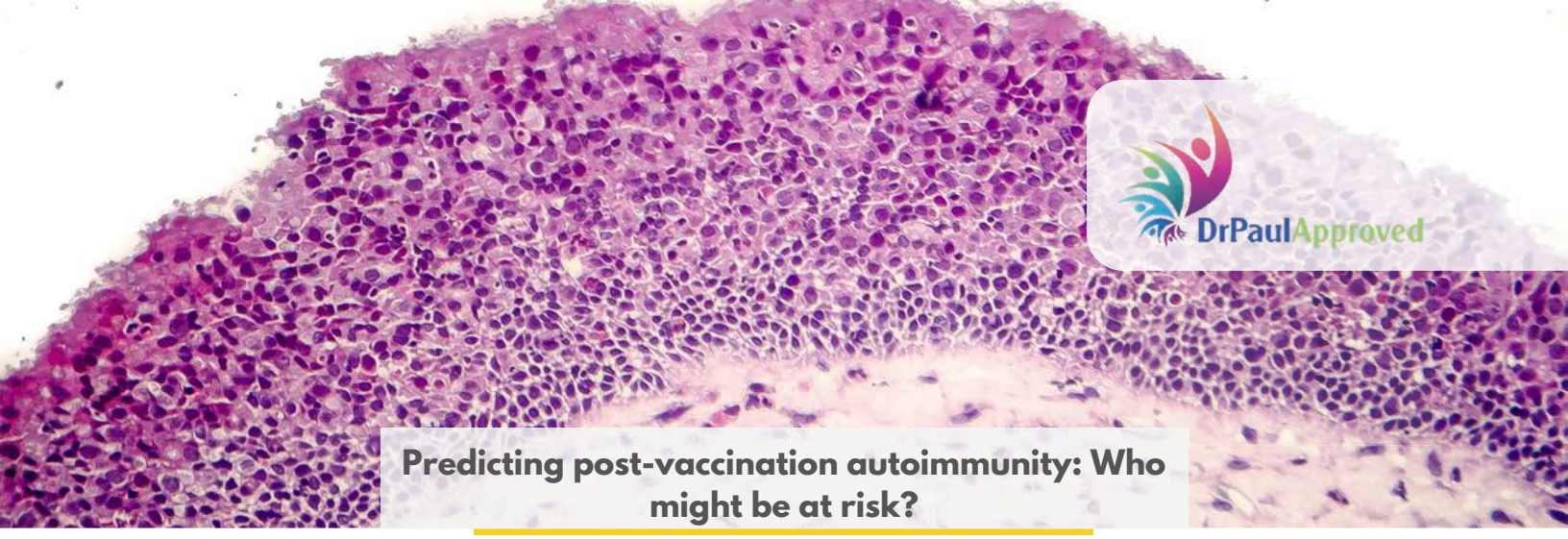
Obesity and Television Watching in Preschoolers in Greece: The GENESIS STUDY

Abstract

The aim of the current work was to evaluate the effect of preschoolers' television (TV) watching time on the prevalence of obesity even after controlling for their total energy intake and their physical activity status. A representative sample of 2,374 Greek children aged 1-5 years was examined ("Growth, Exercise and Nutrition Epidemiological Study in preSchoolers" GENESIS study). Children's TV watching time on a usual weekday and at a usual weekend was recorded. The overall mean of children's TV viewing time was 1.32 h/day. The majority of participants (74.0%) spent <2 h/day watching TV whereas only 3.1% spent >4 h/day in front of a TV set. Overall, 65.2% of participants were normal weight, 17.2% were overweight, and the rest 17.6% were obese. The prevalence of obesity was significantly higher among those with TV viewing time > or = 2 h/day (21.7%) compared to those watching TV <2 h/day (16.1%, P = 0.003). TV viewing time remained significantly associated with the likelihood of being obese even after controlling for potential confounders (i.e., socio demographic and other characteristics and physical activity status) only among children aged 3-5 years. However, further adjusting for children's total energy intake revealed that the association between the TV viewing time and the probability of being obese was no longer statistically significant.

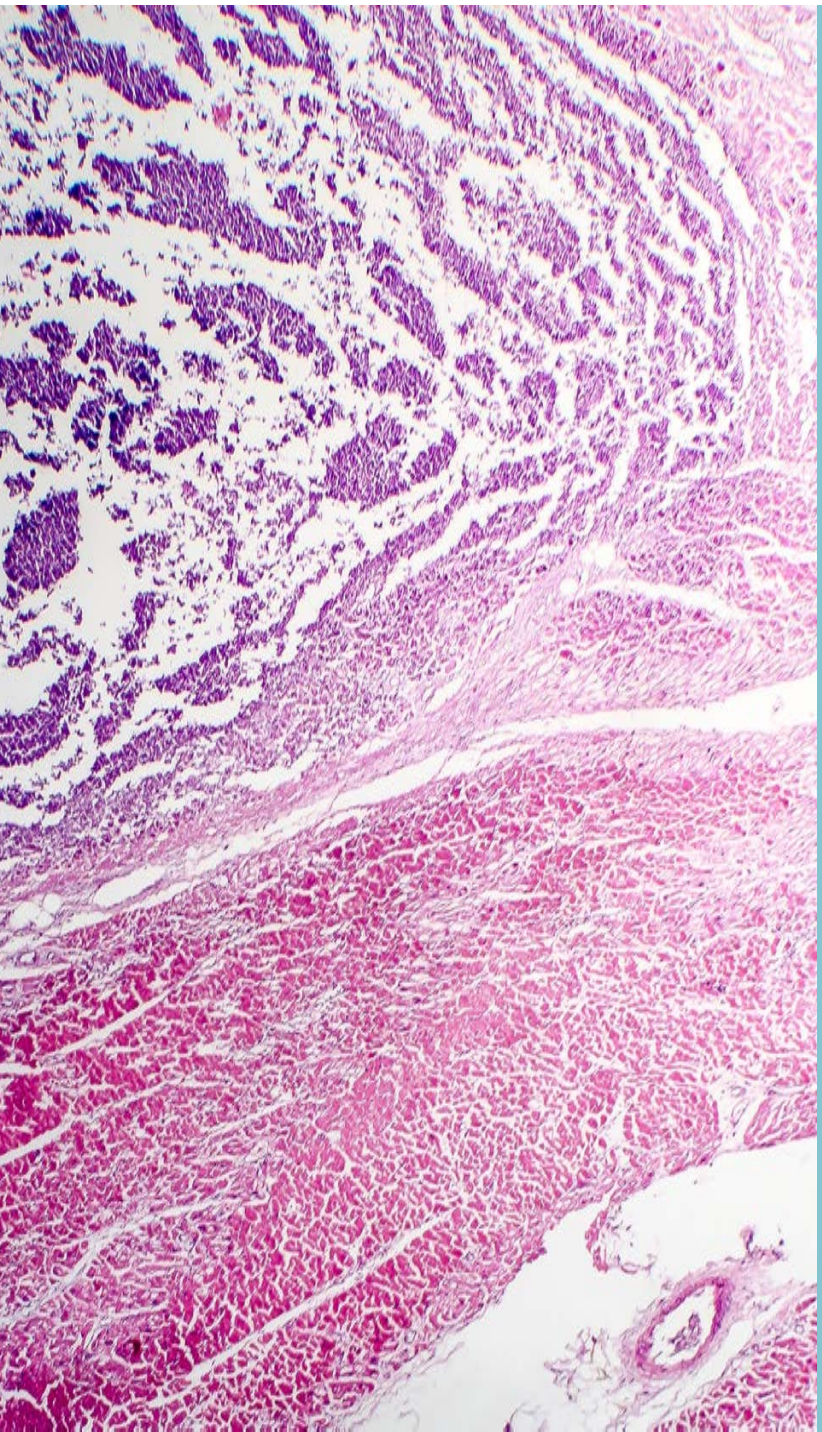
On the other hand, physical activity status continued to be an independent factor of being obese. The current findings support the hypothesis that the effect of TV viewing time on childhood obesity is independent of physical activity status and may be attributed to the increased total energy intake during TV watching.

Citation:
Manios, Yannis, Georgia Kourlaba, Katerina Kondaki, Evangelia Grammatikaki, Anastasia Anastasiadou, and Eleytheria Roma-Giannikou. "Obesity and Television Watching in Preschoolers in Greece: The GENESIS Study." Obesity 17.11 (2009): 2047-053.
http://www.ncbi.nlm.nih.gov/pubmed/19282823



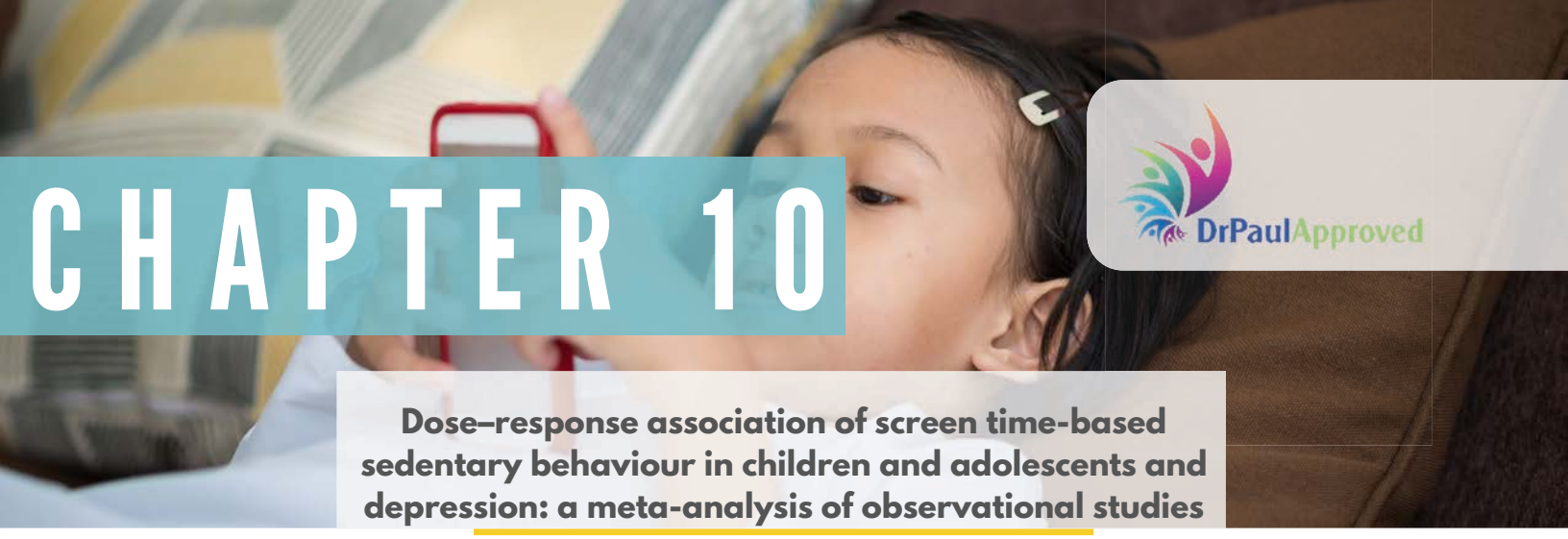
Predicting post-vaccination autoimmunity: Who might be at risk?

Abstract



Vaccinations have been used as an essential tool in the fight against infectious diseases, and succeeded in improving public health. However, adverse effects, including autoimmune conditions may occur following vaccinations (autoimmune/inflammatory syndrome induced by adjuvants--ASIA syndrome). It has been postulated that autoimmunity could be triggered or enhanced by the vaccine immunogen contents, as well as by adjuvants, which are used to increase the immune reaction to the immunogen. Fortunately, vaccination-related ASIA is uncommon. Yet, by defining individuals at risk we may further limit the number of individuals developing post-vaccination ASIA. In this perspective we defined four groups of individuals who might be susceptible to develop vaccination-induced ASIA: patients with prior post-vaccination autoimmune phenomena, patients with a medical history of autoimmunity, patients with a history of allergic reactions, and individuals who are prone to develop autoimmunity (having a family history of autoimmune diseases; asymptomatic carriers of autoantibodies; carrying certain genetic profiles, etc.).

Citation:
Soriano, Alessandra, Gideon Nesher, and Yehuda Shoenfeld. "Predicting Post-vaccination Autoimmunity: Who Might Be at Risk?" Pharmacological Research 92 (2015): 18-22.
http://www.ncbi.nlm.nih.gov/pubmed/25277820



CHAPTER 10

Dose–response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies

Abstract

BACKGROUND:
Depression represents a growing public health burden. Understanding how screen time (ST) in juveniles may be associated with risk of depression is critical for the development of prevention and intervention strategies. Findings from studies addressing this question thus far have been inconsistent. Therefore, we conducted a comprehensive systematic review and meta-analysis of data related to this question.

METHODS:
The meta-analysis was conducted in accordance with the PRISMA guideline. We searched the electronic databases of PubMed, Web of Science and EBSCO systematically (up to 6 May 2015). OR was adopted as the pooled measurement of association between ST and depression risk. Dose–response was estimated by a generalised least squares trend estimation.

RESULTS:
Twelve cross-sectional studies and four longitudinal studies (including 1 cohort study) involving a total of 127 714 participants were included. Overall, higher ST in preadolescent children and adolescents was significantly associated with a higher risk of depression (OR=1.12; 95% CI 1.03 to 1.22). Screen type, age, population and reference category acted as significant moderators. Compared with the reference group who had no ST, there was a non-linear dose–response association of ST with a decreasing risk of depression at ST<2 h/day, with the lowest risk being observed for 1 h/day (OR=0.88; 95% CI 0.84 to 0.93).

CONCLUSIONS:
Our meta-analysis suggests that ST in children and adolescents is associated with depression risk in a non-linear dose–response manner.

Citation:
Liu, M., L. Wu, and S. Yao. "Dose-response Association of Screen Time-based Sedentary Behaviour in Children and Adolescents and Depression: A Meta-analysis of Observational Studies." British Journal of Sports Medicine (2015)
http://bjsm.bmj.com/content/early/2015/11/08/bjsports-2015-095084.short?rss=1

Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression.

Abstract

OBJECTIVE:
Randomized trials of omega-3 polyunsaturated fatty acid (PUFA) treatment for depression have differed in outcome. Recent meta-analyses ascribe discrepancies to differential effects of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) and to diagnostic heterogeneity. This meta-analysis tests the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.

DATA SOURCES:
PubMed/MeSH was searched for studies published in English from 1960 through June 2010 using the terms fish oils (MeSH) AND (depressive disorder [MeSH] OR bipolar depression) AND randomized controlled trial (publication type). The search was supplemented by manual bibliography review and examination of relevant review articles.

STUDY SELECTION:
The search yielded 15 trials involving 916 participants. Studies were included if they had a prospective, randomized, double-blinded, placebo-controlled study design; if depressive episode was the primary complaint (with or without comorbid medical conditions); if omega-3 PUFA supplements were administered; and if appropriate outcome measures were used to assess depressed mood.

DATA EXTRACTION:
Extracted data included study design, sample sizes, doses and percentages of EPA and DHA, mean ages, baseline and endpoint depression ratings and standard deviations for PUFA and placebo groups, and P values. The clinical outcome of interest was the standardized mean difference in the change from baseline to endpoint scores on a depression rating scale in subjects taking PUFA supplements versus subjects taking placebo.

RESULTS:
In a mixed-effect model, percentage of EPA in the supplements was the fixed-effect predictor, dichotomized into 2 groups: EPA < 60% or EPA ⩾ 60% of the total EPA + DHA. Secondary analyses explored the relevance of treatment duration, age, and EPA dose. Supplements with EPA ⩾ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277-0.733; t = 4.195; P < .001) versus supplements with EPA < 60% (effect size = -0.026; 95% CI, -0.200 to 0.148; t = -0.316; P = .756), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA.

CONCLUSIONS:
Supplements containing EPA ⩾ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit.

Citation:
P. Ellis, Amy L. Geant, and J. John Mann. "Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression." J. Clin. Psychiatry The Journal of Clinical Psychiatry 72.12 (2011): 1577-584.
http://www.ncbi.nlm.nih.gov/pubmed/21939614

CHAPTER 11

DrPaulApproved

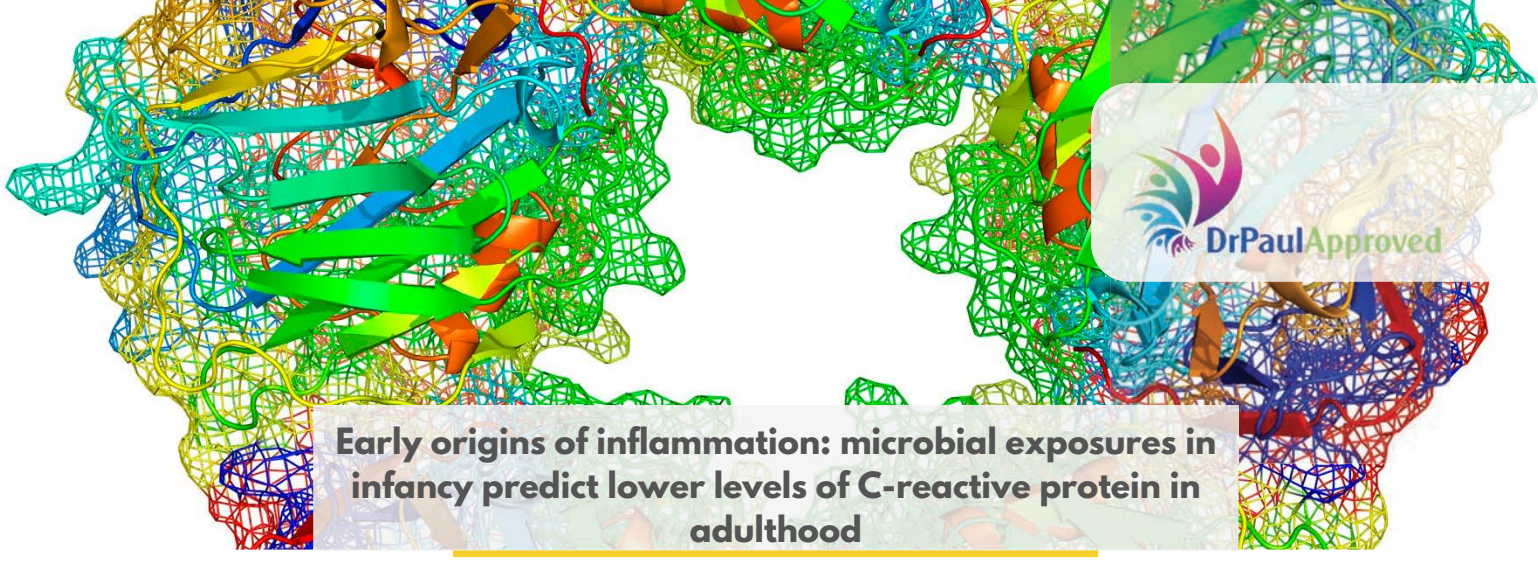
Social laughter is correlated with an elevated pain threshold

Abstract

Although laughter forms an important part of human non-verbal communication, it has received rather less attention than it deserves in both the experimental and the observational literatures.

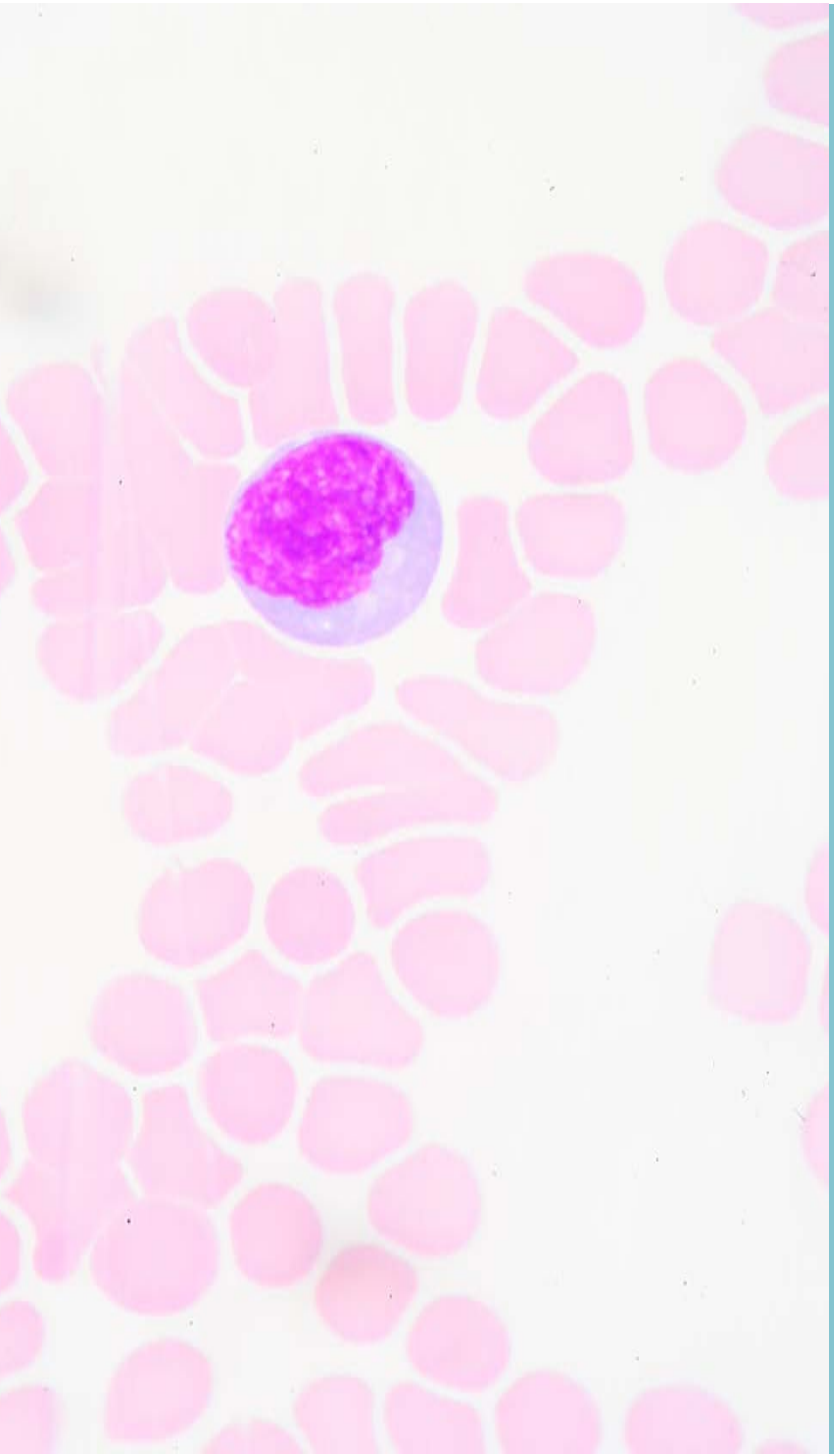
Relaxed social (Duchenne) laughter is associated with feelings of wellbeing and heightened affect, a proximate explanation for which might be the release of endorphins. We tested this hypothesis in a series of six experimental studies in both the laboratory (watching videos) and naturalistic contexts (watching stage performances), using change in pain threshold as an assay for endorphin release. The results show that pain thresholds are significantly higher after laughter than in the control condition. This pain-tolerance effect is due to laughter itself and not simply due to a change in positive affect. We suggest that laughter, through an endorphin-mediated opiate effect, may play a crucial role in social bonding.

Citation:
Dunbar, R. I. M., R. Baron, A. Frangou, E. Pearce, E. J. C. Van Leeuwen, J. Stow, G. Partridge, I. Macdonald, V. Barra, and M. Van Vugt. "Social Laughter Is Correlated with an Elevated Pain Threshold." Proceedings of the Royal Society B: Biological Sciences 279.1731 (2011): 1161-167.
http://rspb.royalsocietypublishing.org/content/279/1731/1161



Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood

Abstract



Ecological factors are important determinants of the development and function of anti-pathogen defences. Inflammation is a central part of innate immunity, but the developmental factors that shape the regulation of inflammation are not known. We test the hypothesis that microbial exposures in infancy are associated with high sensitivity C-reactive protein (CRP) in adulthood using prospective data from a birth cohort in the Philippines (associated with increased CRP, consistent with a role for inflammation in the widely documented n= 1461). Lower birth weight was inverse relationship between birth weight and adult cardiovascular diseases. In addition, higher levels of microbial exposure in infancy were associated with lower CRP. These associations were independent of socioeconomic status, measures of current body fat and other health behaviours. We conclude that measures of microbial exposure and nutrition during the pre-natal and early post-natal periods are important predictors of CRP concentration in young adulthood. We speculate that the development of anti-inflammatory regulatory networks in response to early microbial exposure represents plasticity in the development of anti-pathogen defences, and that this process may help explain the low CRP concentrations in this population.

Citation:
Mcdade, T. W., J. Rutherford, L. Adair, and C. W. Kuzawa. "Early Origins of Inflammation: Microbial Exposures in Infancy Predict Lower Levels of C-reactive Protein in Adulthood." Proceedings of the Royal Society B: Biological Sciences 277.1684 (2009): 1129-137. http://rspb.royalsocietypublishing.org/content/early/2009/12/08/rspb.2009.1795

Preterm Infant Massage Therapy Research: A Review

Abstract

In this paper, preterm infant massage therapy studies are reviewed. Massage therapy has led to weight gain in preterm infants when moderate pressure massage was provided. In studies on passive movement of the limbs, preterm infants also gained significantly more weight, and their bone density also increased. Research on ways of delivering the massage is also explored including using mothers versus therapists and the added effects of using oils. The use of mothers as therapists was effective in at least one study. The use of oils including coconut oil and safflower oil enhanced the average weight gain, and the transcutaneous absorption of oil also increased triglycerides. In addition, the use of synthetic oil increased vagal activity, which may indirectly contribute to weight gain. The weight gain was associated with shorter hospital stays and, thereby, significant hospital cost savings. Despite these benefits, preterm infant massage is only practiced in 38% of neonatal intensive care units. This may relate to the underlying mechanisms not being well understood. The increases noted in vagal activity, gastric motility, insulin and IGF-1 levels following moderate pressure massage are potential underlying mechanisms. However, those variables combined do not explain all of the variance in weight gain, highlighting the need for additional mechanism studies.

Citation:
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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844909/

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Dr. Paul.

Paul Thomas MD

Remember: “If you do what everyone else does, you’ll get the results everyone else is getting.”