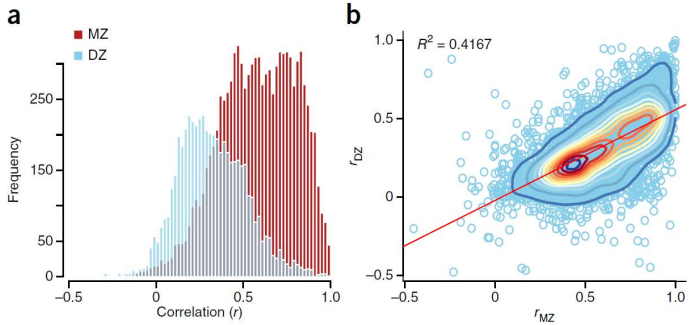
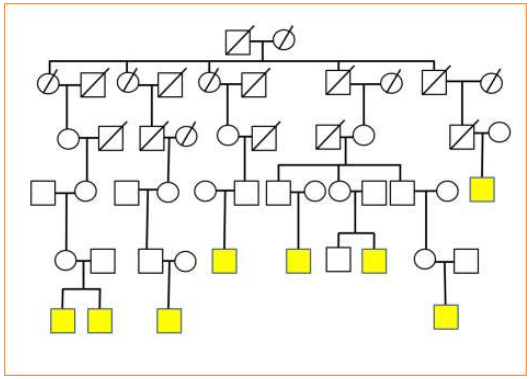
Genetics, Environment, Autism, and the Law

Dr. James Lyons-Weiler, PhD





IPAK






REDUCING HUMAN PAIN AND SUFFERING THROUGH KNOWLEDGE

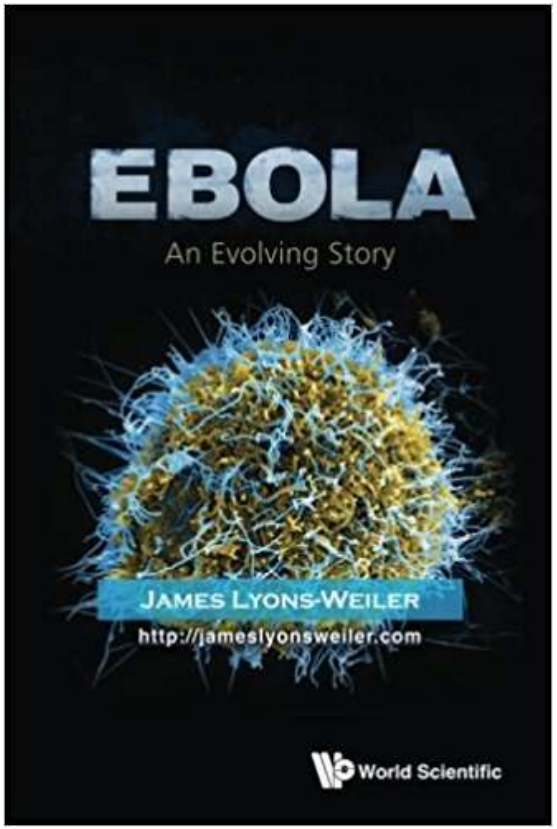
Who Am I?

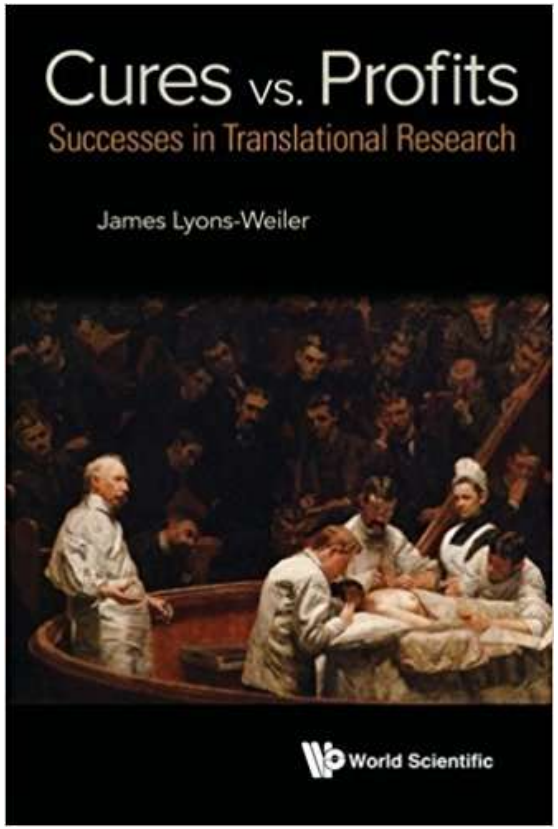
- Biologist, Evolutionary Biologist, Systems Biology Expert,

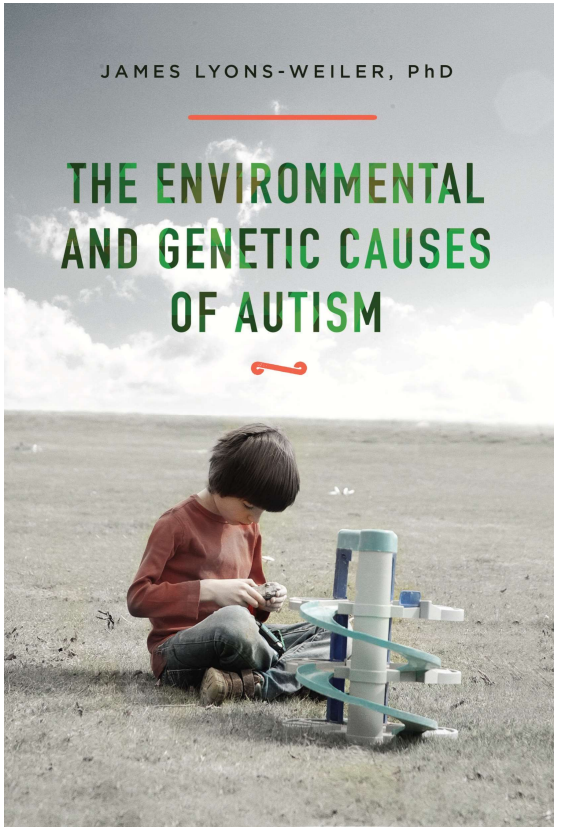
Cancer Biomarkers Research Expert, Bioinformatics Expert

- CEO, Director, Scientist @ The Institute for Pure and Applied Knowledge, a pure public charity research institute that conducts research in the public interest.

Three books (2014-2016)







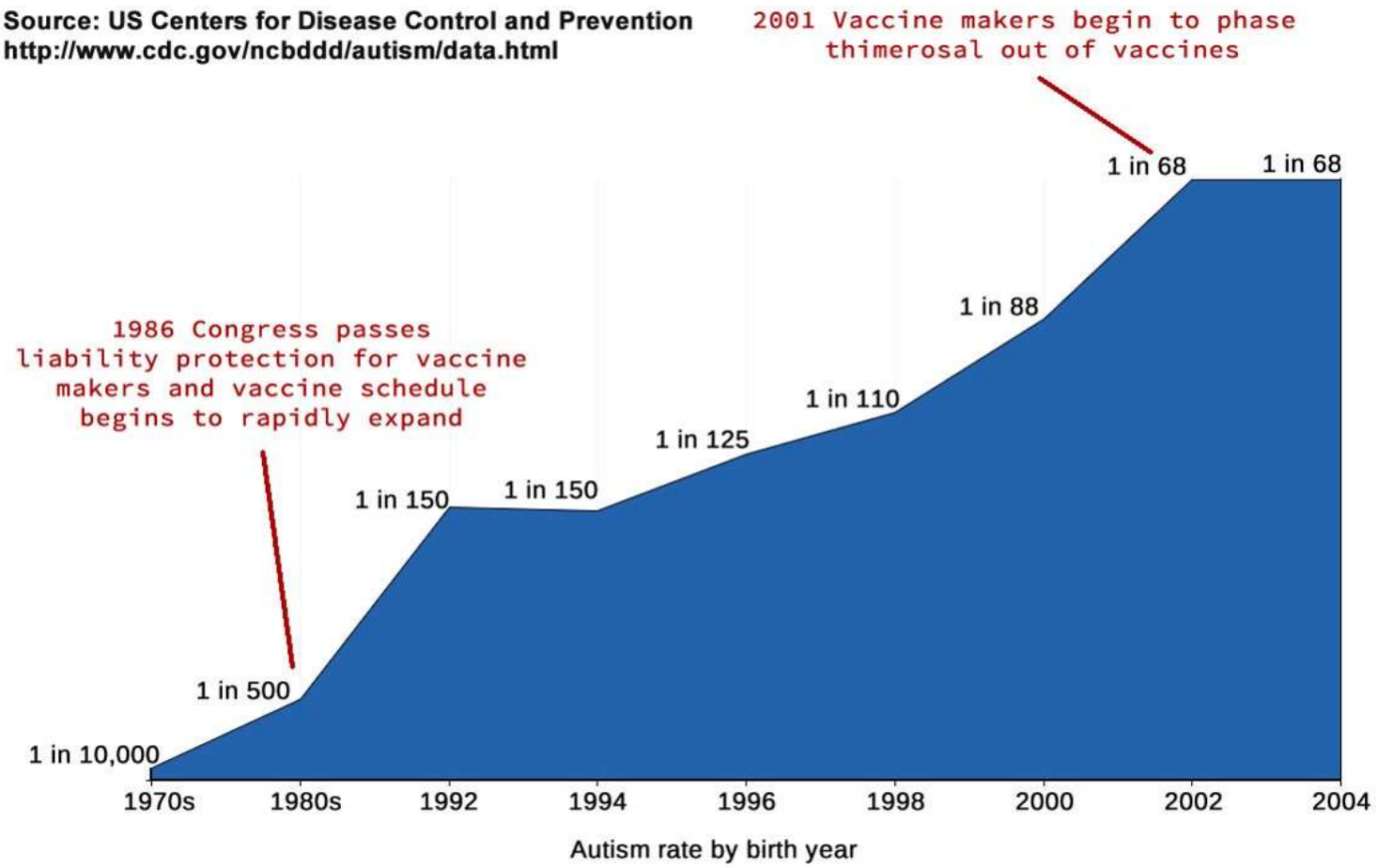
Potential COI Disclosure

- I **do not** receive income from the manufacture, sale, or distribution of vaccines (or any other medical product)
- In 2016, I **was** compensated for consulting effort on two vaccine injury litigations, <$10,000 total
- I **do** receive payment from IPAK from donations from the public, incl. vaccine risk aware individuals.
- IPAK Employees **are not** allowed to personally profit from any intellectual property we generate
- Book proceeds **are** donations to IPAK

NAMES

Mish Michaels loses WGBH science job — because she doesn't believe in vaccines

Autism

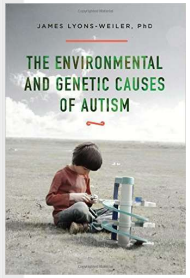

Source: US Centers for Disease Control and Prevention
http://www.cdc.gov/ncbddd/autism/data.html
2001 Vaccine makers begin to phase thimerosal out of vaccines
1986 Congress passes liability protection for vaccine makers and vaccine schedule begins to rapidly expand
1 in 10,000
1 in 500
1 in 150
1 in 150
1 in 125
1 in 110
1 in 88
1 in 68
1 in 68
1970s
1980s
1992
1994
1996
1998
2000
2002
2004
Autism rate by birth year

and PDD-NOS. These conditions differ from each other in degree of severity of symptoms in two core domains.

In DSM-5, three domains of ASD were recognized; in DSM, two have been combined, and thus DSM-5 identifies two domains, as shown in Table 2.

TABLE 2. DOMAINS OF AUTISM SPECTRUM DISORDER

DSM-IV	DSM-5
Social domain	Social/Communication domain
Communication domain	Restrictive, repetitive behaviors
Restrictive, repetitive behaviors	

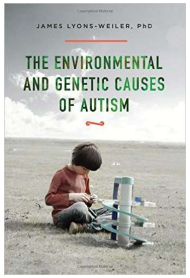


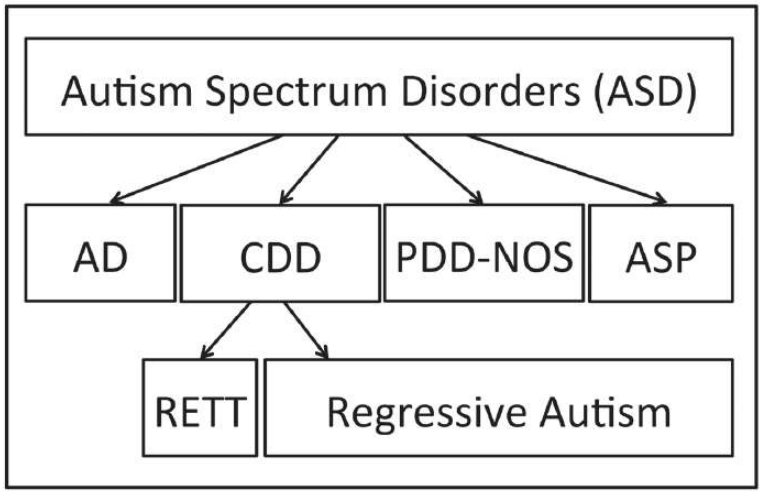
Diagnosis of autism/ASD under DSM requires satisfaction of criteria A–D (from Kaufmann, WE. DSM-5: The New Diagnostic Criteria for Autism Spectrum Disorders. 2012 Symposium):

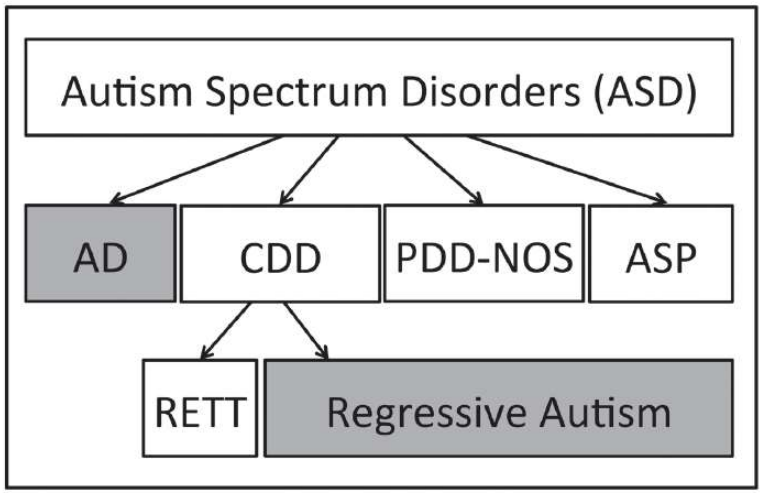
Diagnosis of autism/ASD under DSM requires satisfaction of criteria A–D (from Kaufmann, WE. DSM-5: The New Diagnostic Criteria for Autism Spectrum Disorders. 2012 Symposium):

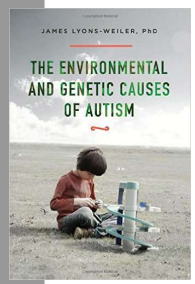
A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays and manifest by all three of the following:
   1. Deficits in social-emotional reciprocity
   2. Deficits in nonverbal communicative behaviors used for social interaction
   3. Deficits in developing and maintaining relationships

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:
   1. Stereotyped or repetitive speech, motor movements, or use of objects.
   2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.







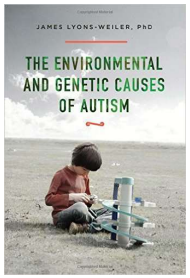


4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment.

C. Symptoms must be present in early childhood* but may not become fully manifest until social demands exceed limited capacities.

D. Symptoms together limit and impair everyday functioning.

*This condition is contradicted elsewhere within DSM-5.



Under DSM-5, if no restrictive, repetitive behaviors are present, social communication disorder may be diagnosed.

A major assumption was made in DSM-5 with a merger of social and communication phenotypes: that the bulk of a lack of social reciprocity is due to deficits in communication skills and not to a domain (of its own). Thus, the loss of speech is technically nudged toward CDD. Because the loss of speech after

Parental Refusal of Childhood Vaccines and Medical Neglect Laws

Efthimios Parasidis, JD, MBioethics, and Douglas J. Opel, MD, MPH

Objectives. To examine the relation of vaccine refusal and medical neglect under child welfare laws.

Methods. We used the Westlaw legal database to search court opinions from 1905 to 2016 and identified cases in which vaccine refusal was the sole or a primary reason in a neglect proceeding. We also delineated if religious or philosophical exemptions from required school immunizations were available at the time of adjudication.

Results. Our search yielded 9 cases from 5 states. Most courts (7 of 9) considered vaccine refusal to constitute neglect. In the 4 cases decided in jurisdictions that permitted religious exemptions, courts either found that vaccine refusal did not constitute neglect or considered it neglect only in the absence of a sincere religious objection to vaccination.

Conclusions. Some states have a legal precedent for considering parental vaccine refusal as medical neglect, but this is based on a small number of cases. Each state should clarify whether, under its laws, vaccine refusal constitutes medical neglect. (*Am J Public Health.* 2017;107:68–71. doi:10.2105/AJPH.2016.303500)

Parental refusal of childhood vaccines is a contentious issue in pediatrics and

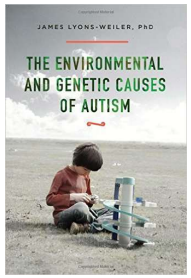
result in harm to the child) constitute child maltreatment.

reports solely based on failure to vaccinate,[6] and Michigan has an explicit policy to this effect.[7] A few states codify that vaccine refusal regardless of reason,[8] or solely for sincere religious beliefs,[9] does not constitute medical neglect. Furthermore, even if vaccine refusal amounts to medical neglect, it is not clear that this finding requires state intervention. Ross and Aspinwall[10] contend that there should be a distinction between medical neglect and state intervention, arguing that vaccine refusal constitutes the former but does not warrant the latter. Chervenak et al.[4] argue that the purpose of reporting parents who refuse childhood vaccines to CPS for neglect is not to provoke "highly intrusive measures," such as loss of custody, but to "engage [CPS] in further efforts to persuade the parents."(p308) Simply invoking CPS, however, may undermine parents' views of

Genetics

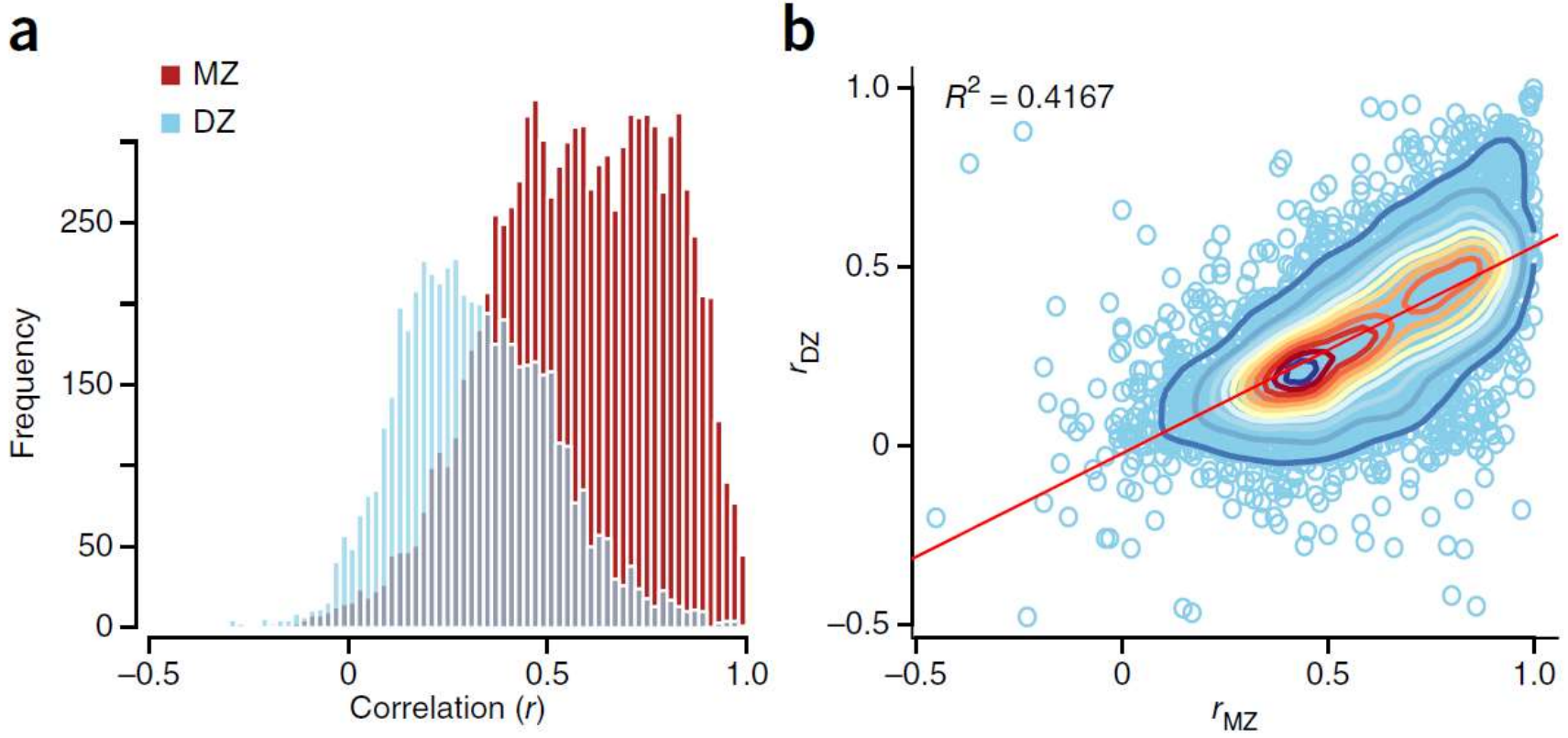
- >850 genes “involved” in Autism
- No individual gene accounts for >1% of ASD
- **20% of autistics have >> Copy Number Variations (CNVs)**
- de Novo variants more common in sporadic vs. familial cases
- **regulatory genes in early development**
- **synaptogenesis throughout life**
- Familial vs. Genetic Risk
- Every mode of inheritance (dominant, recessive, complex)
- Pinto >2-3 affected genes > ASD risk

1. Identical, monozygotic (MZ) twins show a significantly higher concordance of autism diagnosis than fraternal, dizygotic twins for autism, even though siblings grew up together, sharing many environmental influences.
2. No single gene has been found to have a large effect, and studies have resulted in the discovery of numerous genes, clustered in specific pathways, each explaining a minor percentage of cases of autism ASD.
3. First-degree relatives of affected individuals are often found with subthreshold autism or ASD symptoms, indicating that autism and ASD is a heterogeneous, variegated set of conditions, as opposed to a discrete (all/none) genetic disease.



In the terminology of genetics, these observations led to the conclusion that a simple autosomal or X-linked dominant model, or even a recessive mode of monogenic inheritance, was insufficient to describe the patterns of inheritance of risk of autism. They pointed to autism risk as a complex trait, involving many loci and many genes, with likely interactions among genes (epistasis). However,

Heritability, >2,000,000 estimates (any human traits): 1958-2012 (Polderman et al.)



Phenomimicry: Some cases disrupted mutations, others by environmental exposure

- CHD7, CHD8 – neural crest, early development
  - LOF mutations vs. Valproaic acid
- Mutations in ER genes, Thimerosal inhibition of ERAP1
- Mitochondrial mutations vs. Glyphosate-induced mitopathy
- Microglial cell modulation of MAO-A, LoF mutations in MAO-A
- LOF mutation ANY protein-encoding gene, autoimmunity

Finding mutations
does not rule out environment

Functional Groups by Age

- -9 mo to 0 years

Early (pre-natal) regulatory genes
CHD7, CHD8 (neural crest, neurogenesis)

- 0- 2years

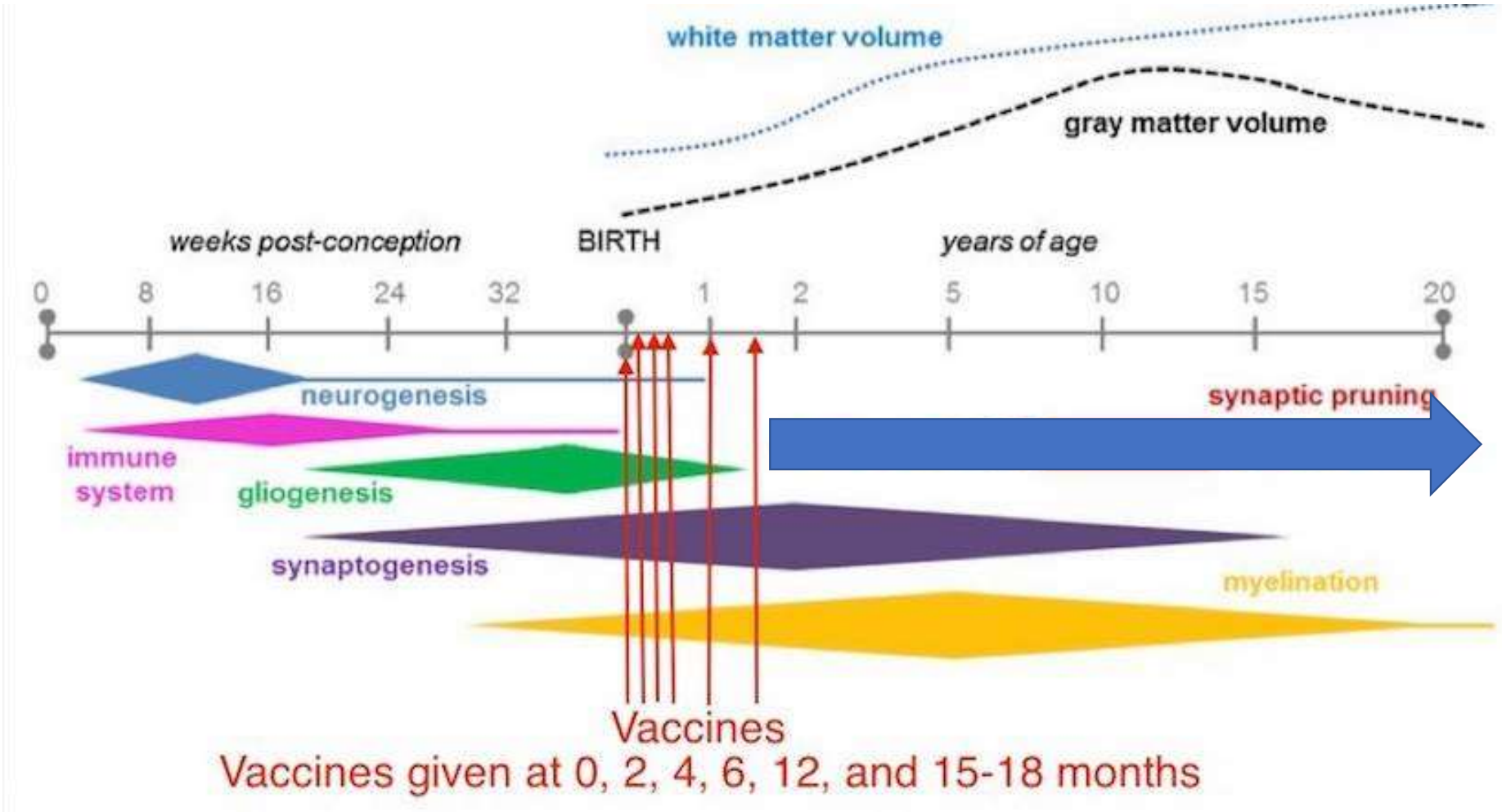
Peri/post-natal brain development
Synaptogenesis, PRUNING

- 2-4 years

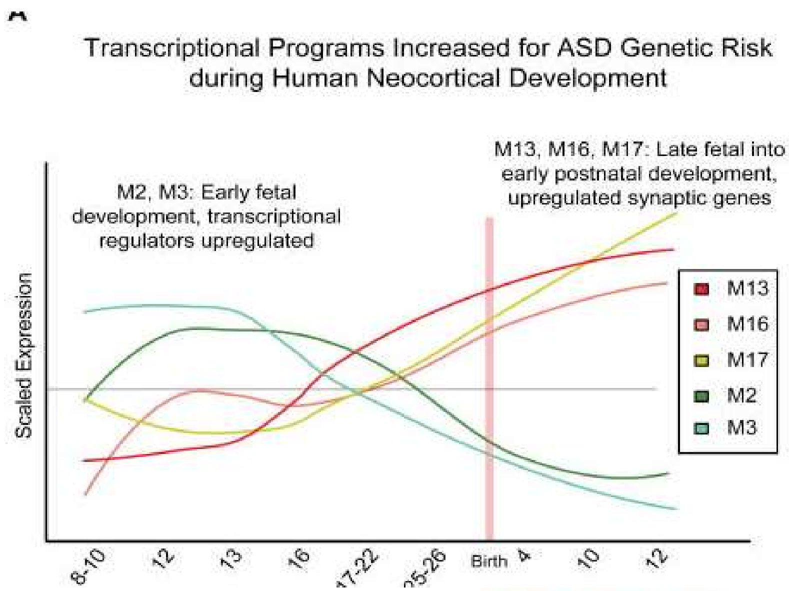
PRUNING, MYELINATION

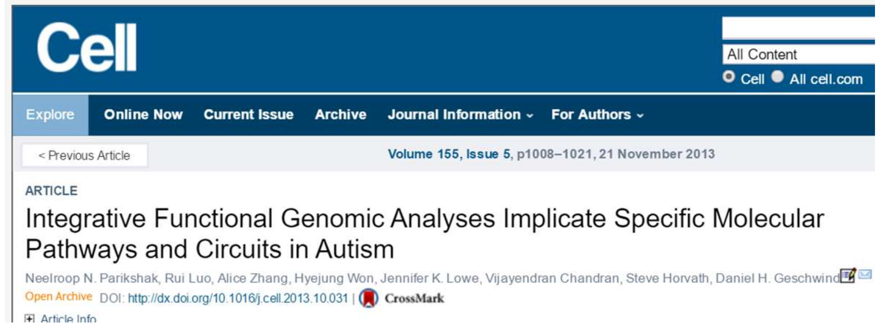
- Lifetime

Synaptic proteins
Glutamate receptors
Serotonin receptors (e.g., SCN1A)
Cellular detox proteins (ERAP1)
Mitochondrial genes (ROS)



Vaccines given at 0, 2, 4, 6, 12, and 15-18 months

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ARTICLE
Integrative Functional Genomic Analyses Implicate Specific Molecular Pathways and Circuits in Autism
Neelroop N. Parikshak, Rui Luo, Alice Zhang, Hyejung Won, Jennifer K. Lowe, Vijayendran Chandran, Steve Horvath, Daniel H. Geschwind
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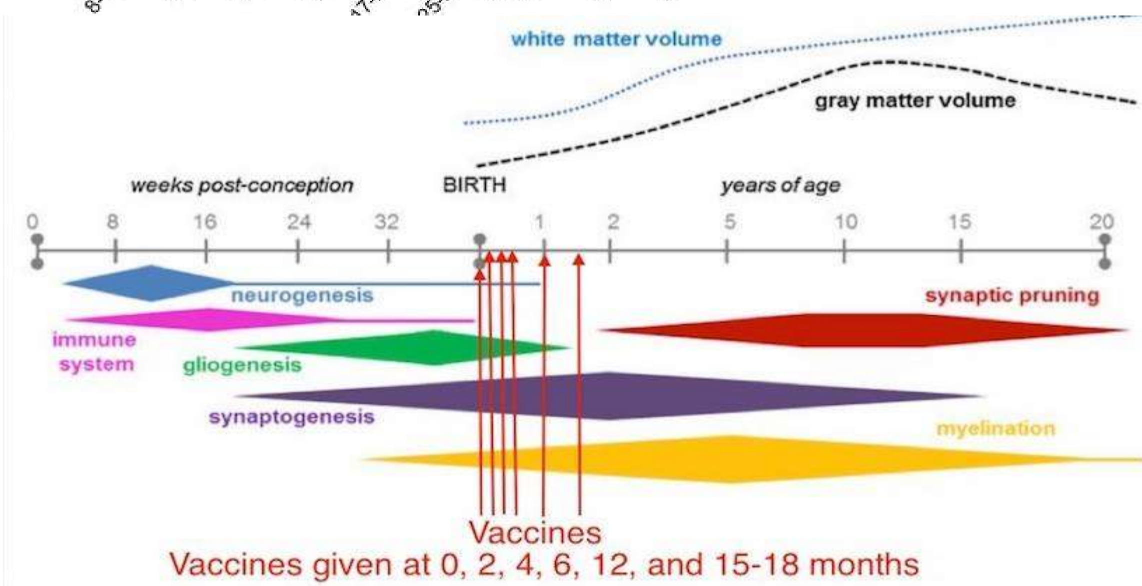

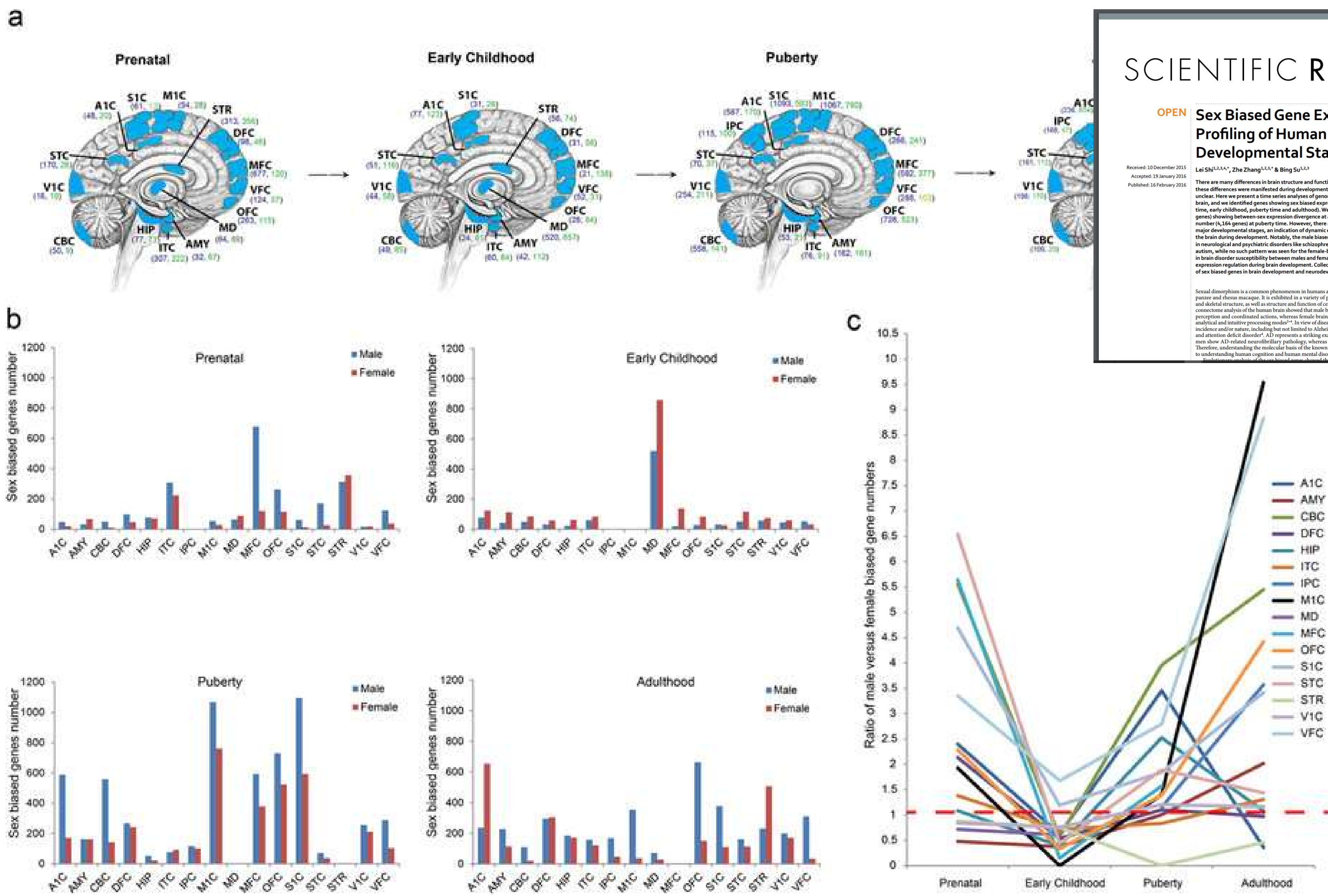

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Sex Biased Gene Expression Profiling of Human Brains at Major Developmental Stages

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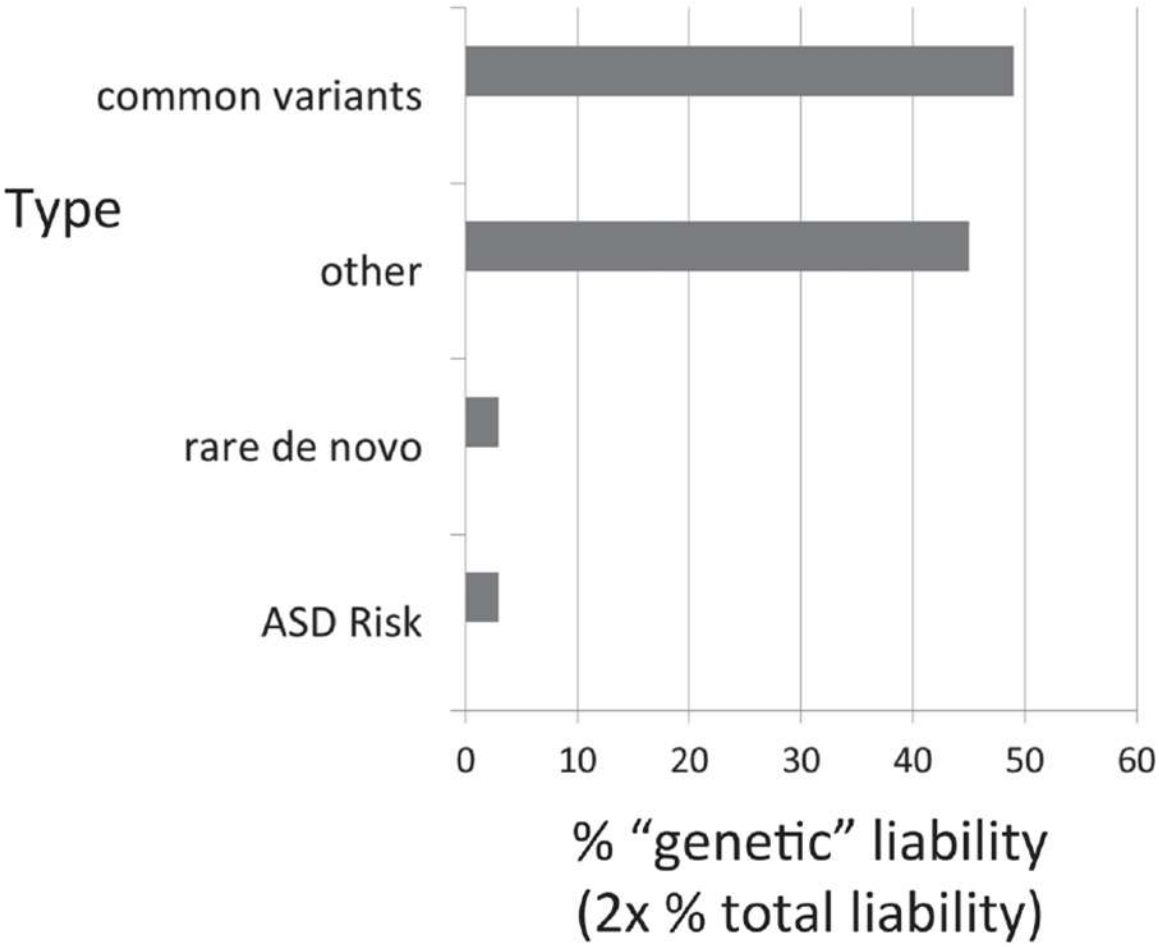
Lei Shi[1,2,3,4,*], Zhe Zhang[1,2,3,*] & Bing Su[1,2,3]

There are many differences in brain structure and function between males and females. However, how these differences were manifested during development and maintained through adulthood are still unclear. Here we present a time series analyses of genome-wide transcription profiles of the human brain, and we identified genes showing sex biased expression at major developmental stages (prenatal time, early childhood, puberty time and adulthood). We observed a great number of genes (>2,000 genes) showing between-sex expression divergence at all developmental stages with the greatest number (4,164 genes) at puberty time. However, there are little overlap of sex-biased genes among the major developmental stages, an indication of dynamic expression regulation of the sex-biased genes in the brain during development. Notably, the male biased genes are highly enriched for genes involved in neurological and psychiatric disorders like schizophrenia, bipolar disorder, Alzheimer's disease and autism, while no such pattern was seen for the female-biased genes, suggesting that the differences in brain disorder susceptibility between males and females are likely rooted from the sex-biased gene expression regulation during brain development. Collectively, these analyses reveal an important role of sex biased genes in brain development and neurodevelopmental disorders.

Sexual dimorphism is a common phenomenon in humans and many non-human primate species, such as chimpanzee and rhesus macaque. It is exhibited in a variety of physical characteristics, such as body size, hair color and skeletal structure, as well as structure and function of central nervous system (CNS)[1]. For example, structural connectome analysis of the human brain showed that male brains are structured to facilitate connectivity between perception and coordinated actions, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes[2–4]. In view of disease, many CNS disorders show sex differences in their incidence and/or nature, including but not limited to Alzheimer's disease (AD), schizophrenia, autism, addiction and attention deficit disorder[4]. AD represents a striking example of between-sex difference. Up to 90% of older men show AD-related neurofibrillary pathology, whereas it is found in only 8–10% of age-matched women[4]. Therefore, understanding the molecular basis of the known sex differences of the brain is of obvious importance to understanding human cognition and human mental disorders.



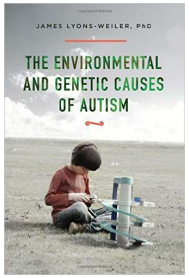
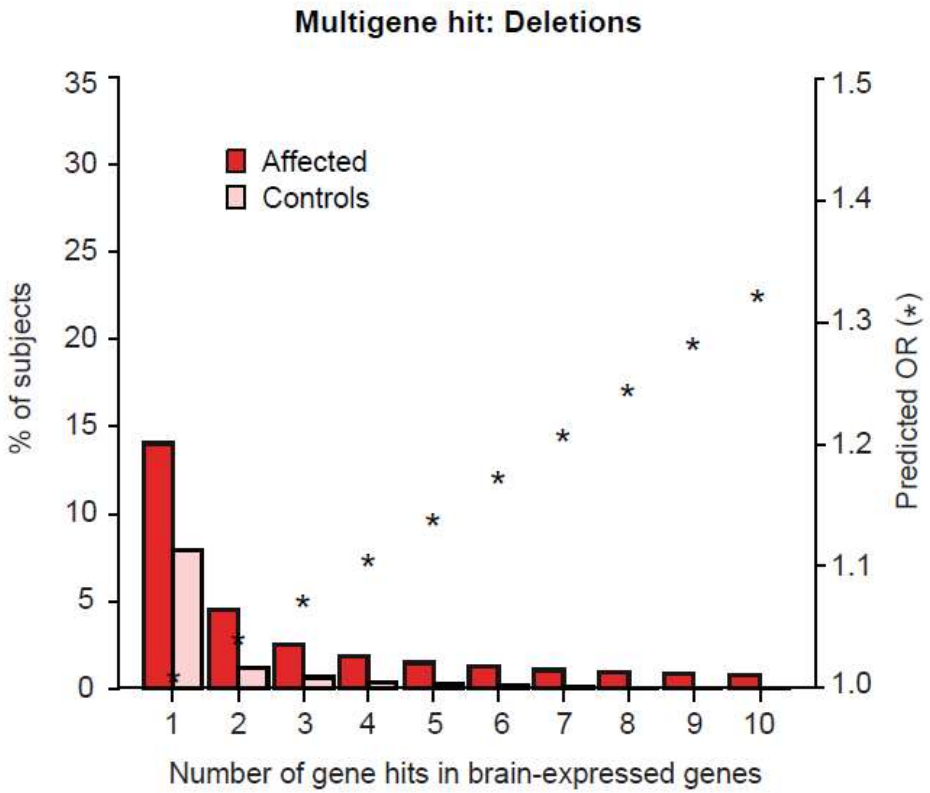
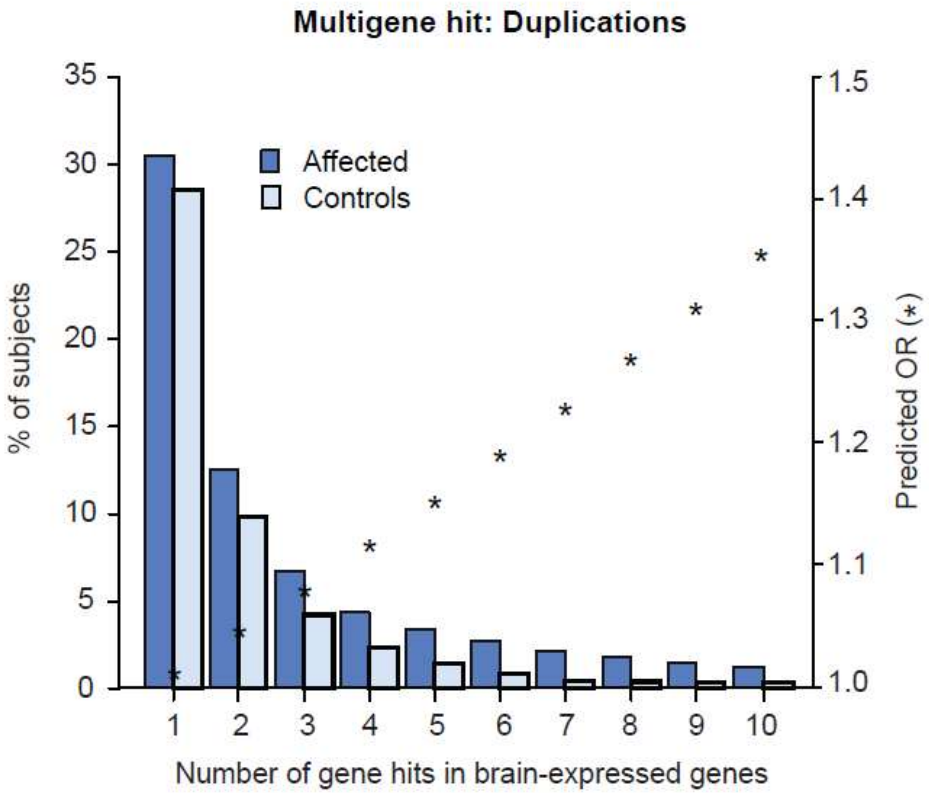


Figure 2. Percent "genetic" liability contributed by mutation class type (estimates from Gaugler et al., 2014). Pure "genetic" ASD and de novo variation represent the least amount of liability. Common variants set the stage and are thus not "autism" genes;

Pinto et al


Multigene hit: Deletions
Affected
Controls
% of subjects
Predicted OR (*)
Number of gene hits in brain-expressed genes


Multigene hit: Duplications
Affected
Controls
% of subjects
Predicted OR (*)
Number of gene hits in brain-expressed genes

Largest Genetic Studies (Hallmayer, 2011; Sandin, 2014)

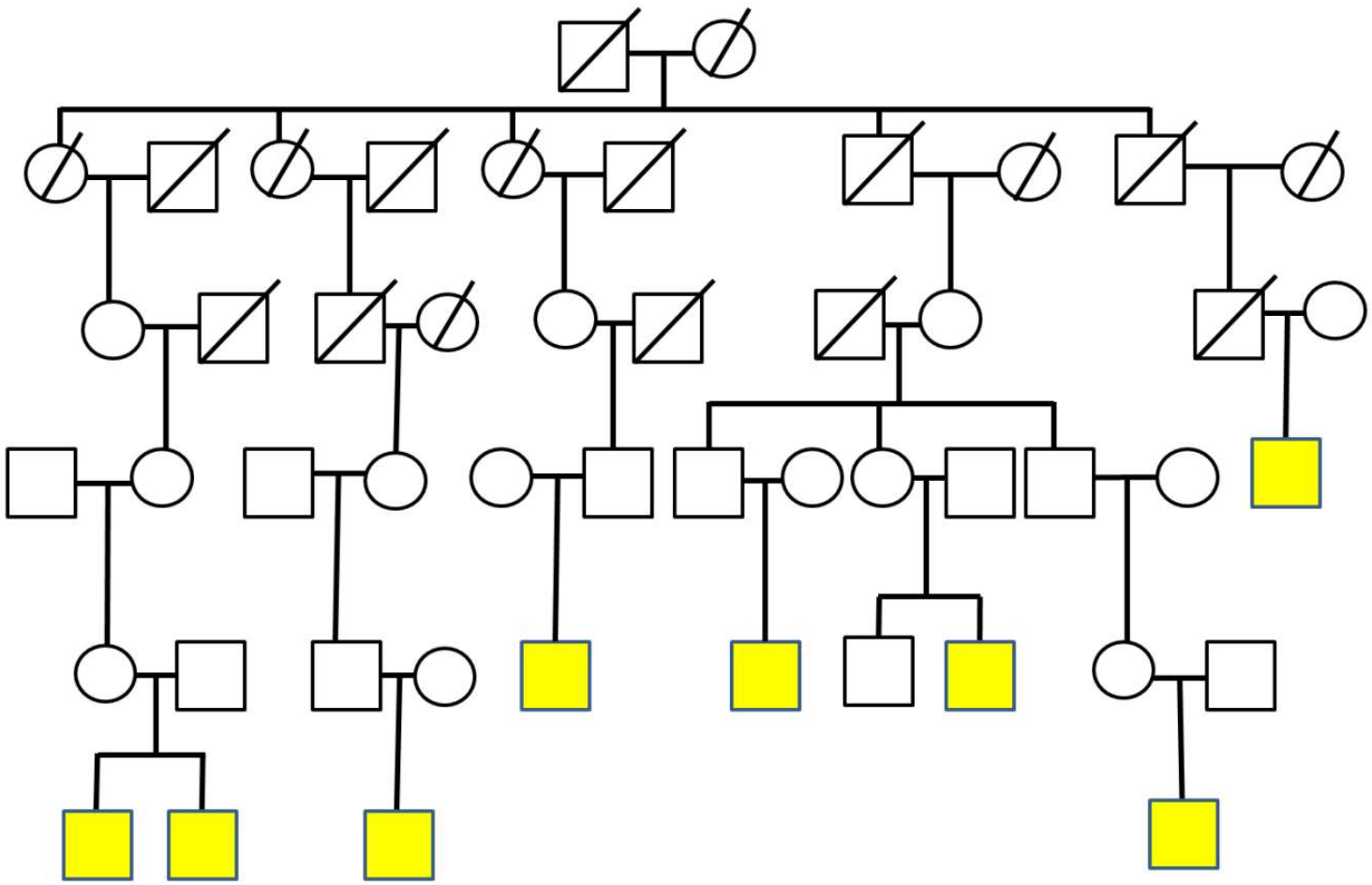
- Did not measure any environmental factors
- Did not estimate G x E interactions
- Both concluded around **50% E, 50% G**

MZ, DZ, G%, E%, missing%

Source	MZ	DZ
Tick 5%	98%	53%
Tick 1%	98%	67%

Broad-sense heritability 67-94%, shared E, 7-35%

Source	%G	%E	%missing
Hallmayer	38(h2)	58	4
Sandin	46	54	0
Colvert	56	30	8

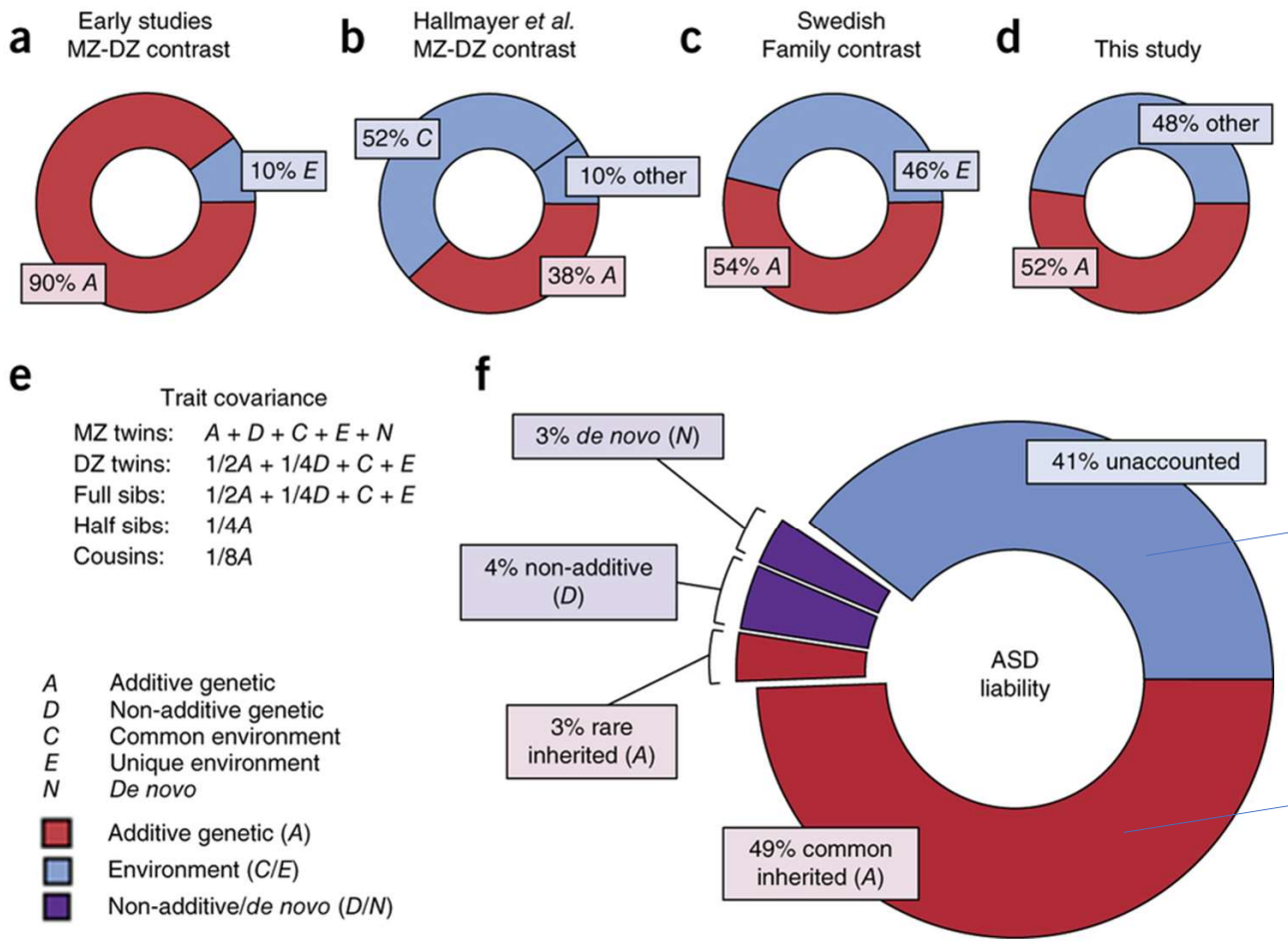


Implies low narrow-sense heritability h2 (approx. h2 = 0)

New Studies

- People who self-identify as being on the spectrum tend to have kids w/ASD traits – regardless of diagnosis.

- Evans D.W. *et al. J. Am. Acad. Child Adolesc. Psychiatry* **56**, 51-58 (2017) **PubMed**
- Losh M. *et al. J. Autism Dev. Disord.* Epub ahead of print (2017) **PubMed**

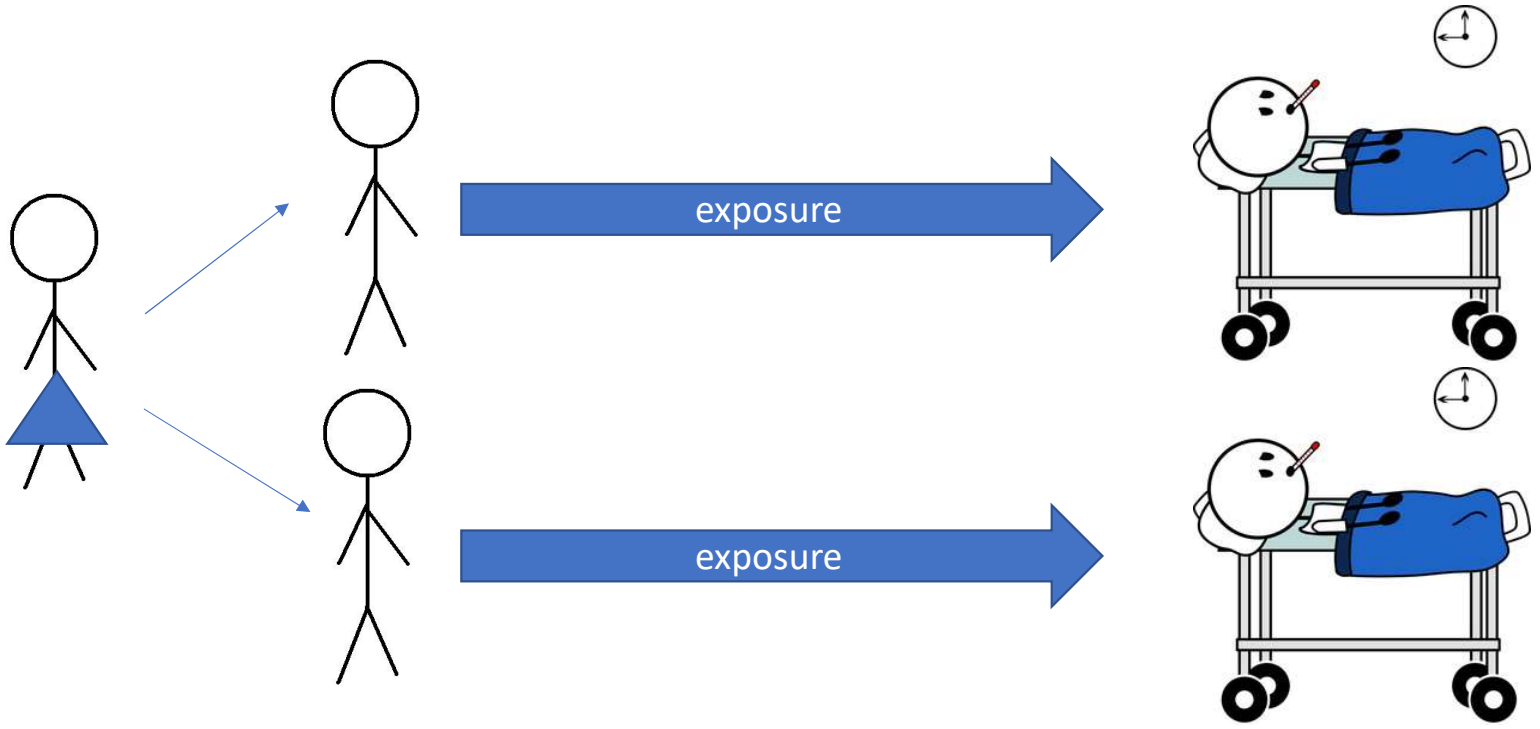


Environment,
G x E,
and
Gene x gene
Interactions

Inherited common,
Universal
environment

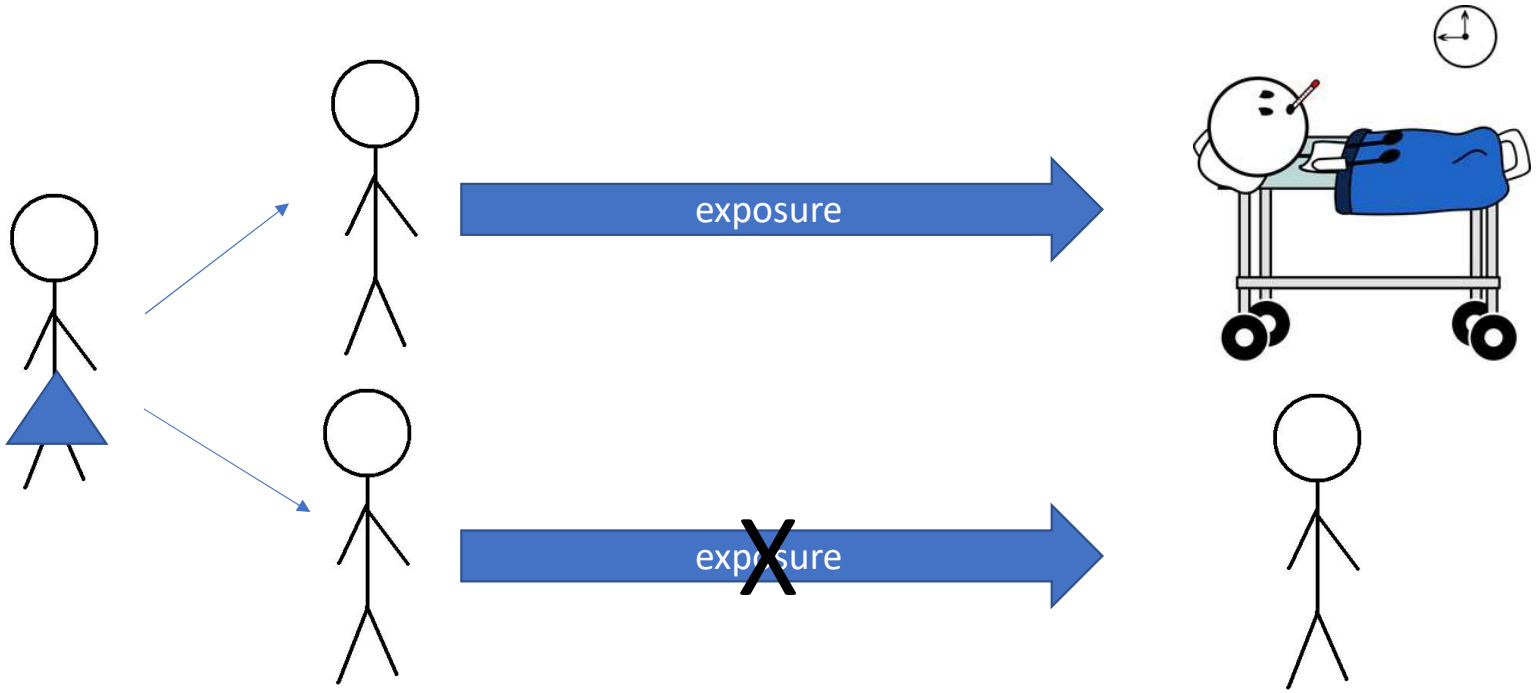
Gaugler T et al.
Most genetic risk for autism resides with common variation.
Nat Genet. 2014 Aug;46(8):881-5. doi: 10.1038/ng.3039. Epub 2014 Jul 20.

“Reproducibility of Environment Effects in Twins” Shared Environment Interpretation



Environmental susceptibility will look like **common variation** if the correct environmental factors are not studied.

“Reproducibility of Environment Effects in Twins” Unique Environment Studies Needed



Environmental susceptibility will look like **common variation** if the correct environmental factors are not studied.

G x E Interactions
Bowers & Erickson (2014) Review

- Organophosphates <-> *PON1* gene
- Pregnancy-related stress <-> *ADRB2* gene
- Traffic-related particulate matter (pollution) <-> *MET* gene

- Periconceptional maternal prenatal vitamin <-> (*MTHFR, CBS, COMT*)

- Bowers K, C. Erickson. 2014. Gene-environment interaction and autism spectrum disorder. OA Autism 2(1):3.

Additional evidence of G x E

- **Rose et al.** Mercury damage in autism may be mediated via mitochondrial dysfunction in some
- **Choi et al.** Maternal immune activation leads to (IL-17a) activation -> abnormal cortical phenotype
- **Hadley et al., 2014.** Glutamate receptors and transporters (mGluR gene network > 270 genes) – autistics have more CNV's than neurotypicals
- **Nayak et al. 2002.** Protein malnutrition may influence the specific manifestation of aluminum-induced neurotoxicity
- **Numerous studies** – Lifelong microglial activation

Evidence of Specific G x E in Vaccines

- Sodium channel gene SCN1A variation associated with sensitivity to vaccine-induced encephalopathy (O'Roak et al. 2011)

- MTHFR mutations ⬆ Thimerosal susceptibility (Austin, 2014)

Phenomimicry: Some cases disrupted mutations, others by environmental exposure

- CHD7, CHD8 – neural crest, early development
  - LOF mutations vs. Valproaic acid
- Mutations in ER genes, Thimerosal inhibition of ERAP1
- Mitochondrial mutations vs. Glyphosate-induced mitopathy
- Microglial cell modulation of MAO-A, LoF mutations in MAO-A
- LOF mutation ANY protein-encoding gene, autoimmunity

Individual Genes

- ASD Risk Genes (< 1%)
  - Synaptic proteins (>70), GABA-B3 receptor, Shank2/3 TSC1/2 MECP2 PTEN dup(16p11), **CNTNAP2**

- **Environmental Susceptibility Genes (40-60%)**
  - Glutamate receptors, endoplasmic reticulum proteins, cellular detoxification pathway proteins

- Autism Phenotype Modifier Genes (40%; communication skills, intellect)
  - FoxP1, serotonin transporters

Schasfma et al. 2017

- Genetics: CNTAP2
- Gender: (M/F)
- MIA (LPS + Bacterial infection)

> Current Issue > vol. 114 no. 6 > Sara M. Schaafsma, 1383–1388, doi: 10.1073/pnas.1619312114

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Sex-specific gene–environment interactions underlying ASD-like behaviors

Sara M. Schaafsma[a,1,2], Khatuna Gagnidze[a], Anny Reyes[a], Natalie Norstedt[a], Karl Månsson[a], Kerel Francis[a], and Donald W. Pfaff[a,2]

Author Affiliations

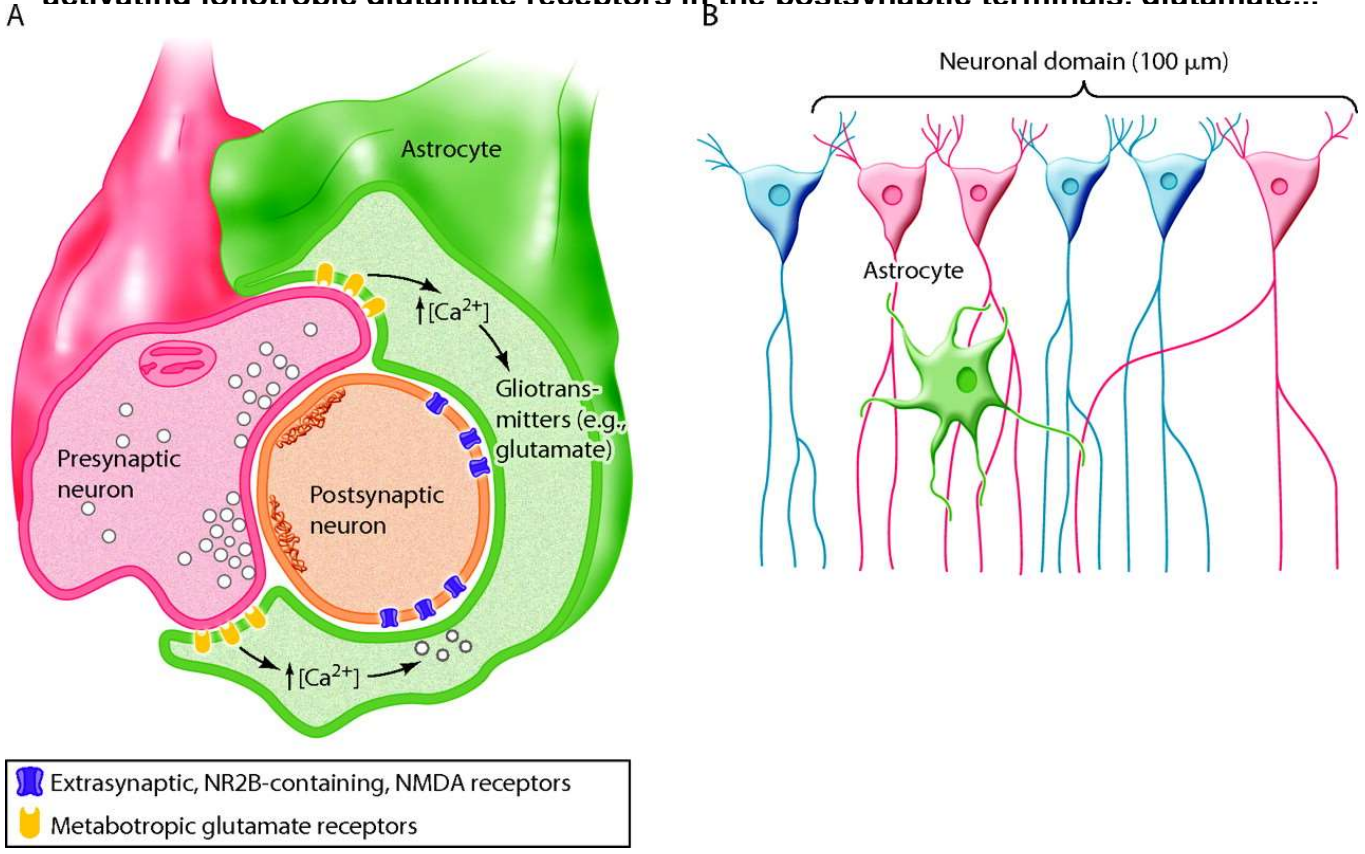
Abstract

The male bias in the incidence of autism spectrum disorders (ASDs) is one of the most notable characteristics of this group of neurodevelopmental disorders. The etiology of this sex bias is far from known, but pivotal for

Three Hit Categories

Dependent Variable	*p*
Vocalizations	<0.001
Social recognition	0.047
Habituation	0.211
Dishabituation	0.099
CRH expression	0.08
H3K4me3	0.011

Glutamate released from hippocampal astrocytes induces neuronal synchrony through the activation of extrasynaptic NR2B-containing NMDA receptorsA: in the hippocampus, besides activating ionotropic glutamate receptors in the postsynaptic terminals, glutamate...



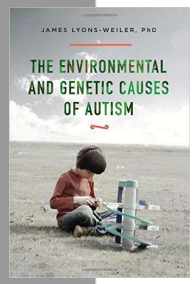
Tommaso Fellin et al. Physiology 2006;21:208-215

Physiology

SPEECH, MICROGLIA, AND NERVE CELL EXTENSION ROLES IN LOSS-OF-FUNCTION MUTATIONS

Loss-of-function (LoF) driven pathway analysis revealed three major clusters of functionally aggregate gene modules in ASD (Liu et al., 2014), reflecting functional groups involved in the following:

- Speech and language, clustering around the gene FOXP2.
- Microglial activation, clustering around the gene PTEN.
- Microtubule-processes in nerve cell function, clustering around the gene SPAST.



The importance of FOXP2 and PTEN in ASD has been discussed previously in this book. The SPAST cluster found by Liu et al. (2014) may indicate the importance of a microtubule reorganization, which is important for both cell shape development (neurite extension and neuronal arborization) and microglial and astrocyte functioning. Another effect could be disruption of the modulation of the endoplasmic reticulum, important for cellular waste transport and detoxification. Mutations in genes in this cluster could lead to sequestration of toxins in cells such as astrocytes (disrupting glutamate uptake) and microglia, which hinder proper mediation of synapses and autophagy.

Genes Organized by Contribution to ASD Phenotype (examples)

• **"ASD"**	CHD8, KATNAL2, 5-HT2A receptor, 16p11.2 dup/del,
• **"Autism severity"**	MOA-B
• **Neural development**	CHD7
• **Macrocephaly**	PTEN
• **Language ability**	16p11.2 CNVs, 5-HT2RA, FOXP1
	mitochondrial dysfunction
• **Intellectual ability**	SHANK genes, Glutamate receptor genes, BDNF, MAO-A, 5-HT2A serotonin receptor
• **Social Function/Affective Knowledge**	OXTR, DD4R
• **Repetitive behaviors**	SLC25A12
• **Hypersensitivity to sound**	CNTN5, CNTN6
• **Aggression**	MOA-A CD13
• **Severity of Depression**	rs6311

Environmental Factor (Known and Suspected)

- Congenital Rubella Inf.
- Aluminum
- Mercury
- Acetaminophen
- Monosodium glutamate
- Thalidomide
- Valproic acid
- Glyphosate
- PBDEs (flame retardant)
- Air pollution
- Phthalates
- Ultrasound exposure
- Solvents (parental exposure)

Examples of Evidence of Environmental Liability

↑ mercury amalgam		Holmes et al., 2003
↑ maternal immune activation		Many sources
↑ acetominophen after MMR		Schultz et al., 2008
		Bauer et al., 2003
↑ autoantibodies to the folate receptor protein is related to neural tube defects and autism	→	Molecular mimicry
aluminum causes apoptosis of motor		Shaw and Petrik (2009)
↓ Serum levels of Vit D_3		Feng et al. (2016)

- May also reflect genetic risk

CAROLINE A. MACERA San Diego State University, USA

MING JI San Diego State University, USA

ABSTRACT The present study was performed to determine whether acetaminophen (paracetamol) use after the measles-mumps-rubella vaccination could be associated with autistic disorder. This case-control study used the results of an online parental survey conducted from 16 July 2005 to 30 January 2006, consisting of 83 children with autistic disorder and 80 control children. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic disorder when considering children 5 years of age or less (OR 6.11, 95% CI 1.42–26.3), after limiting cases to children with regression in development (OR 3.97, 95% CI 1.11–14.3), and when considering only children who had post-vaccination sequelae (OR 8.23, 95% CI 1.56–43.3), adjusting for age, gender, mother's ethnicity, and the presence of illness concurrent with measles-mumps-rubella vaccination. Ibuprofen use after measles-mumps-rubella vaccination was not associated with autistic disorder. This preliminary study found that acetaminophen use after measles-mumps-rubella vaccination was associated with autistic disorder.

KEYWORI
acetamin
phe
autisı
paracetam
vaccinati

ADDRESS Correspondence should be addressed to: DR STEPHEN SCHULTZ, 943 Water Thrush Court, Antioch, Illinois 60002, USA. e-mail: Stephen.schultz@med.navy.mil or stevendri@hotmail.com

DOI: 10.1177/1362361307089518

71% of kids with RA had an episode of fever > 101°F
In 33% of these cases, the fever occurred *right after vaccination* (Shoffner et al., 2010)

Children with more severe autism had larger amounts of circulating anti-brain protein antibodies (Piras et al.. 2014)

Acetaminophen use in p

Secure | https://academic.oup.com/ije/article-abstract/doi/10.1093/ije/dyw115/2617189/Acetaminophen-use-in-pregnancy-and?redirectedFrom=fulltext

International Journal of Epidemiology

IEA

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"**Conclusions:** Prenatal acetaminophen exposure was associated with a greater number of autism spectrum symptoms in males and showed adverse effects on attention-related outcomes for both genders. These associations seem to be dependent on the frequency of exposure."

Article Contents

2016

Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptom

Claudia B. Avella-Garcia; Jordi Julvez
Isolina Riaño Galán; Adonina Tardón;
Show more

Int J Epidemiol dyw115. **DOI:** https:
Published: 28 June 2016 **Article hi**

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Autism. 2008 May;12(3):293-307. doi: 10.1177/1362361307089518.

Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder: the results of a parent survey.

Schultz ST[1], Klonoff-Cohen HS, Wingard DL, Akshoomoff NA, Macera CA, Ji M.

Author information

2008

Abstract

The present study was performed to determine whether acetaminophen (paracetamol) use after the measles-mumps-rubella vaccination could be associated with autistic disorder. This case-control study used the results of an online parental survey conducted from 16 July 2005 to 30 January 2006, consisting of 83 children with autistic disorder and 80 control children. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic disorder when considering children 5 years of age or less (OR 6.11, 95% CI 1.42-26.3), after limiting cases to children with regression in development (OR 3.97, 95% CI 1.11-14.3), and when considering only children who had post-vaccination sequelae (OR 8.23, 95% CI 1.56-43.3), adjusting for age, gender, mother's ethnicity, and the presence of illness concurrent with measles-mumps-rubella vaccination. Ibuprofen use after measles-mumps-

Ask me anything

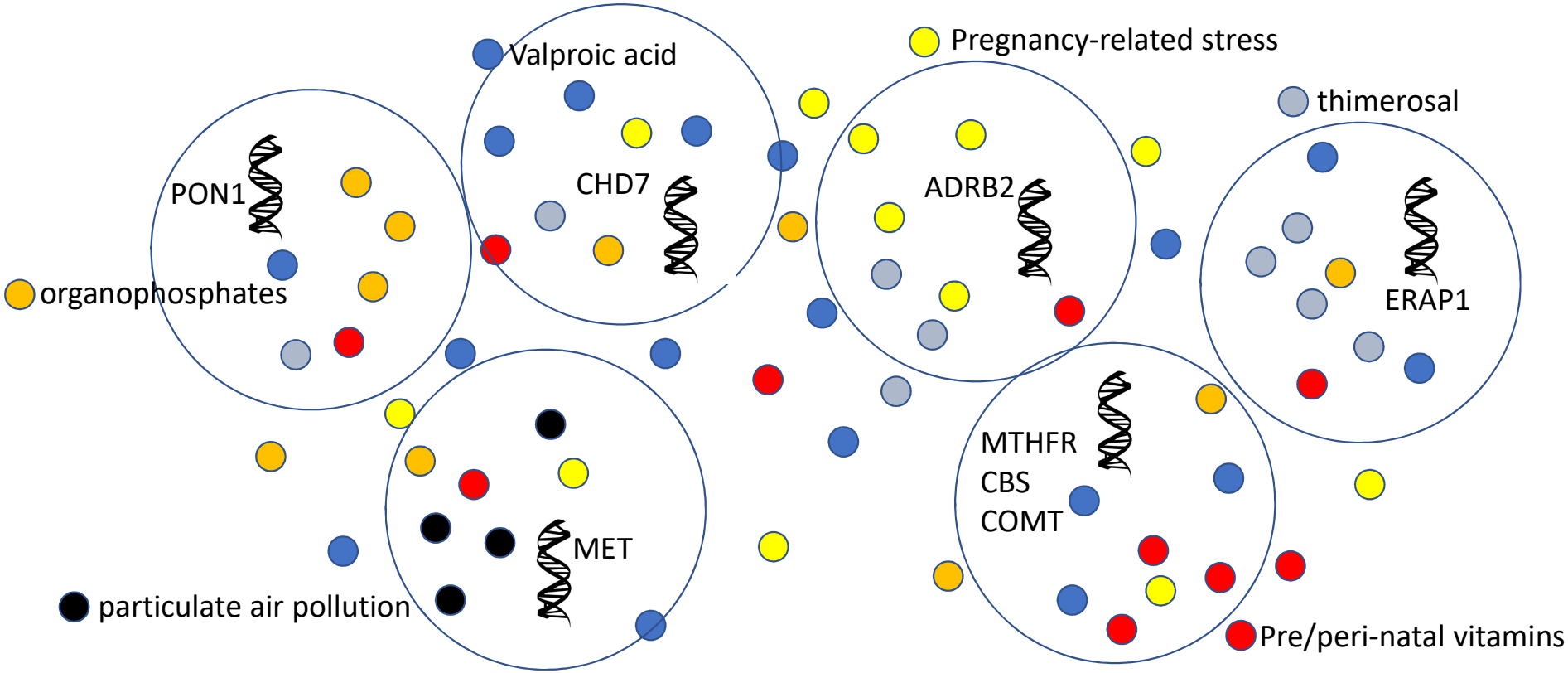
Autism is No More than 50% Genetic, at Least 50% Environmental (Likely more)

- Important open questions:

- Where do the >> de novo CNV in ASD come from?

- Do they predispose some families to increased genetic susceptibility to environmental toxins?

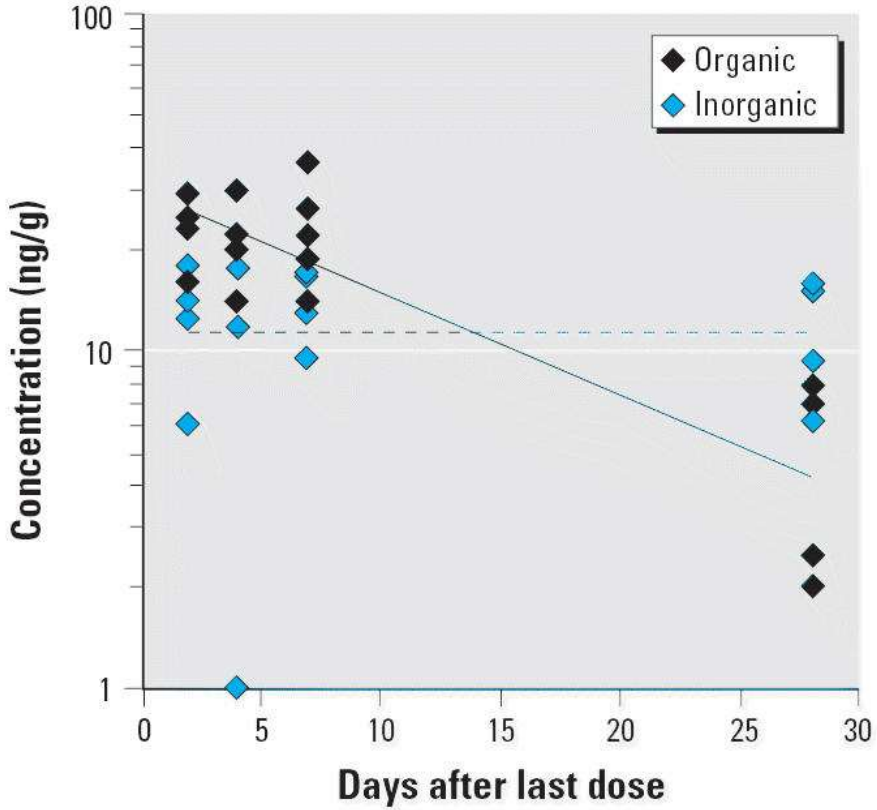
Environmental Toxin Liability Sampling Theory



Burbacher et al.

- **Ethyl mercury stays in organs (including the brain) longer than methyl mercury**

Demonstrates that previous notions of faster clearance of ethyl mercury cf. methyl were *mistaken.*



"Evidence from such studies point to a half-life of inorganic mercury in human brains of several years to several decades" Rooney Toxicology and Applied Pharmacology Volume 274, Issue 3, 1 February 2014, Pages 425–435

Inorganic mercury Half-life: 27 years

ERAP1

ACS Medicinal Chemistry Letters

Letter

pubs.acs.org/acsmedchemlett

Screening Identifies Thimerosal as a Selective Inhibitor of Endoplasmic Reticulum Aminopeptidase 1

Athanasios Stamogiannos,[†,‡] Athanasios Papakyriakou,[†,‡] Francois-Xavier Mauvais,[§] Peter van Endert,[§] and Efstratios Stratikos[*,†]

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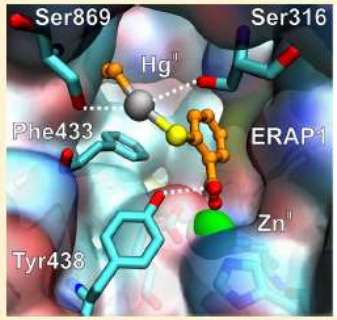
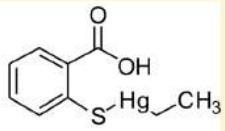
[§]Institut National de la Santé et de la Recherche Médicale, Unité1151; Université Paris Descartes, Sorbonne Paris Cité; Centre National de la Recherche Scientifique, Unité 8253, 75015 Paris, France

Supporting Information

ABSTRACT: We employed virtual screening followed by *in vitro* evaluation to discover novel inhibitors of ER aminopeptidase 1, an important enzyme for the human adaptive immune response that has emerged as an attractive target for cancer immunotherapy and the control of autoimmunity. Screening hits included three structurally related compounds carrying the (*E*)-*N*′-((1*H*-indol-3-yl)methylene)-1*H*-pyrazole-5-carbohydrazide scaffold and (2-carboxylatophenyl)sulfanyl-ethylmercury as novel ERAP1 inhibitors. The latter, also known as thimerosal, a common component in vaccines, was found to inhibit ERAP1 in the submicromolar range and to present strong selectivity versus the homologous aminopeptidases ERAP2 and IRAP. Cell-based analysis indicated that thimerosal can effectively reduce ERAP1-dependent cross-presentation by dendritic cells in a dose-dependent manner.





7, Thimerosal

ERAP1	**0.24 μM**
ERAP2	>50 μM
IRAP	>50 μM
LAP	>50 μM

KEYWORDS: *ERAP1, ERAP2, IRAP, aminopeptidase, inhibitor, immune system, antigenic peptide, docking*

Endoplasmic reticulum (ER) aminopeptidases generate antigenic peptides for loading onto Major Histocompat-

knowledge-based virtual screening approaches, taking advantage of key structural characteristics revealed in the recent crystal

Toxicology and Applied Pharmacology 274 (2014) 425–435

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Invited Review Article

The retention time of inorganic mercury in the brain — A systematic review of the evidence

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Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College, 152-160 Pearse Street, Dublin 2, Ireland

ARTICLE INFO

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Available online 22 December 2013

Keywords:
Mercury
Half-life

ABSTRACT

Reports from human case studies indicate a half-life for inorganic mercury in the brain in the order of years—contradicting older radioisotope studies that estimated half-lives in the order of weeks to months in duration. This study systematically reviews available evidence on the retention time of inorganic mercury in humans and primates to better understand this conflicting evidence. A broad search strategy was used to capture 16,539 abstracts on the Pubmed database. Abstracts were screened to include only study types containing relevant information. 131 studies of interest were identified. Only 1 primate study made a numeric estimate for the half-life of inorganic mercury (227–540 days). Eighteen human mercury poisoning cases were followed up long term including autopsy. Brain inorganic mercury concentrations at death were consistent with a half-

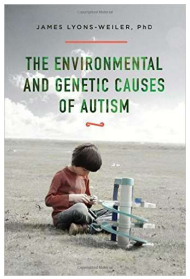
* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875								

Vaccine	Aluminum Content (ug)* per dose	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16-18 yrs
Hepatitis B1 (HepB)	250	1st dose		2nd dose		3rd dose											
Rotavirus2 (RV)				1st dose	2nd dose												
RV1 (2-dose series); RV5 (3-dose series)																	
Diphtheria, tetanus, & acellular pertussis3 (DTaP: <7 yrs)	625			1st dose	2nd dose	3rd dose				←4th dose→			5th dose				
Haemophilus influenzae type b4 (Hib)	225			1st dose	2nd dose			←3rd or 4th dose,									
Pneumococcal conjugate5 (PCV13)	125			1st dose	2nd dose	3rd dose		←4th dose→									
Inactivated poliovirus6 (IPV:<18 yrs)				1st dose	2nd dose	←3rd dose→							←4th dose→				
Influenza7 (IIV; LAIV)						Annual vaccination (IIV only) 1 or 2 doses				Annual vaccination (IIV only) 1 or 2 doses		Annual vaccination (IIV only) 1 or 2 doses			Annual vaccination (IIV only) 1 or 2 doses		
Measles, mumps, rubella8 (MMR)							1st dose						2nd dose				
Varicella9 (VAR)								1st dose					2nd dose				
Hepatitis A10 (HepA)	250							1st dose		2nd dose							
Meningococcal11 (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)															1st dose		
Tetanus, diphtheria, & acellular pertussis12 (Tdap: ≥7 yrs)															(Tdap)		
Human papillomavirus13 (2vHPV:females only; 4vHPV, 9vHPV:males and females)															(3 dose series)		
Meningococcal B11																	
Pneumococcal polysaccharide5 (PPSV23)																	
	* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875							

Aluminum

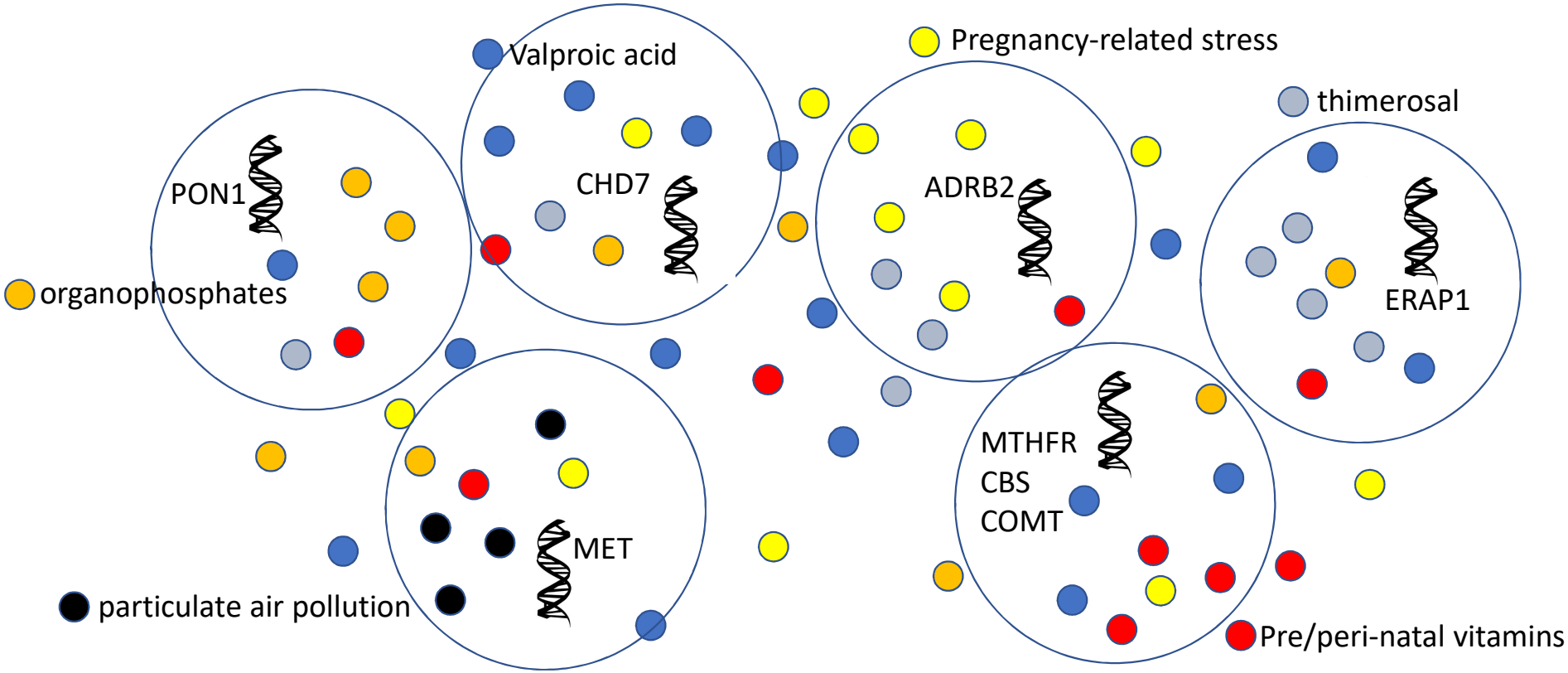
- HepB  250 μg per dose (750 μcg source)
- HepA  250 μg per dose (500 μcg source)
- DTaP  625 μg per dose (3,125 μcg source)
- HiB  225 μg per dose (900 μcg source)
- PCV  125 μg per dose (500 μcg source)

5,775 μg (typical schedule)



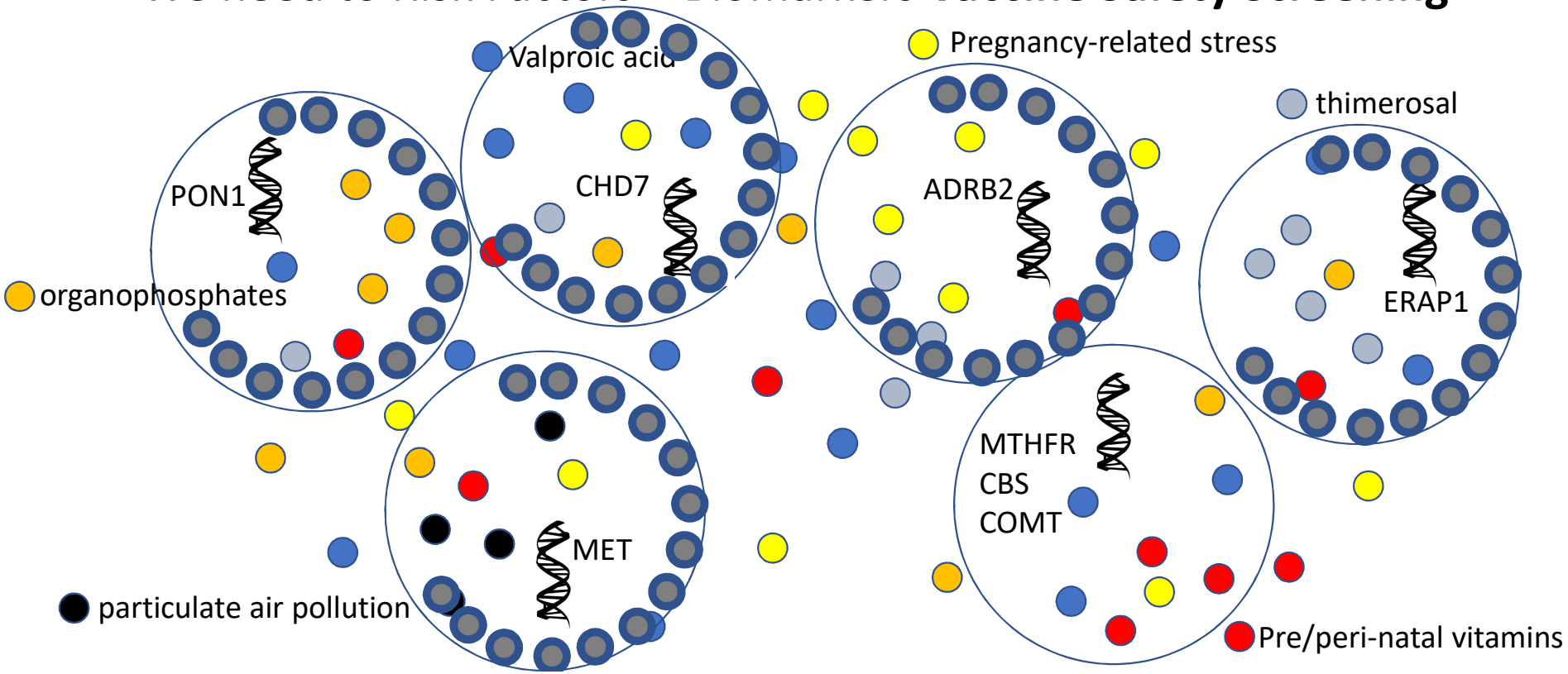
"The toxic effects of aluminum are best described as widespread and pernicious. Inside the cell, aluminum shuts down the transcription of protein-coding genes and miRNA genes in two ways, via direct and specific interaction with H1 linker histones and by suppressing global gene expression by down-regulating RNA polymerase II (see review in Bhattacharjee, 2013). ***Aluminum causes a buildup of glial fibrillary acid protein (GFAP) filaments near the cell nucleus*** *and destruction of the actin cytoskeleton (Theiss et al., 2002). Structural effects of aluminum in rodents include the appearance of neurofibrillary tangles that resemble those from Alzheimer's patients (Uemura et al., 1984; Somova et al., 1997)."*

Environmental Toxin Liability Sampling Theory



Environmental Toxin Liability Sampling Theory

- Aluminum levels in vaccines are unsafe
- We need to Risk Factors + Biomarkers **Vaccine Safety Screening**



OPEN ACCESS Freely available online

PLOS ONE

Aluminium Induced Endoplasmic Reticulum Stress Mediated Cell Death in SH-SY5Y Neuroblastoma Cell Line Is Independent of p53

Syed Husain Mustafa Rizvi[1], Arshiya Parveen[1], Anoop K. Verma[2], Iqbal Ahmad[3], Md Arshad[4], Abbas Ali Mahdi[1]*

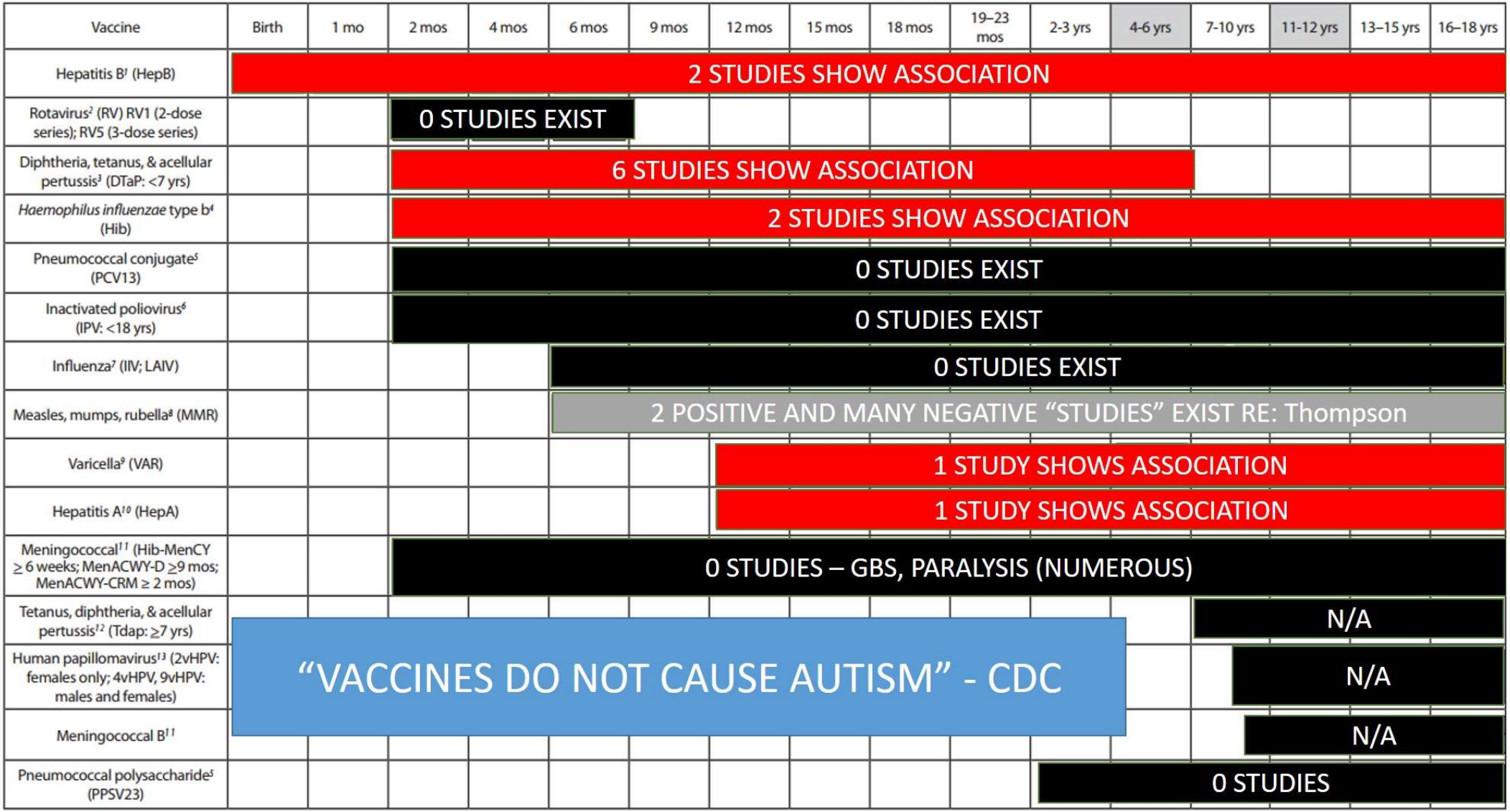
1 Department of Biochemistry, King George's Medical University, Lucknow, Uttar Pradesh, India, **2** Forensic Medicine & Toxicology, King George's Medical University, Lucknow, Uttar Pradesh, India, **3** Fibre Toxicology Division, CSIR- Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India, **4** Department of Zoology, Lucknow University, Lucknow, Uttar Pradesh, India

Abstract

Aluminium (Al) is the third most abundant element in the earth's crust and its compounds are used in the form of house hold utensils, medicines and in antiperspirant etc. Increasing number of evidences suggest the involvement of Al^{+3} ions in a variety of neurodegenerative disorders including Alzheimer's disease. Here, we have attempted to investigate the role of Al in endoplasmic reticulum stress and the regulation of p53 during neuronal apoptosis using neuroblastoma cell line. We observed that Al caused oxidative stress by increasing ROS production and intracellular calcium levels together with depletion of intracellular GSH levels. We also studied modulation of key pro- and anti-apoptotic proteins and found significant alterations in the levels of Nrf2, NQO1, pAKT, p21, Bax, Bcl2, Aβ1-40 and Cyt c together with increase in endoplasmic reticulum (ER) stress related proteins like CHOP and caspase 12. However, with respect to the role of p53, we observed downregulation of its transcript as well as protein levels while analysis of its ubiquitination status revealed no significant changes. Not only did Al increase the activities of caspase 9, caspase 12 and caspase 3, but, by the use of peptide

“NO STUDY HAS EVER SHOWN”

- [x] ANALYZE THE DATA REPEATEDLY UNTIL THE POSITIVE ASSOCIATION “GOES AWAY”
- [x] CHANGE THE RESULTS POST-PEER REVIEW, POST-PUBLICATION, IN PLAIN SITE (UNO ET AL.)
- [x] USE THE MOST CONSERVATIVE METHOD FOR MULTIPLE HYPOTHESIS TESTING (BONFERRONI)
- [x] CHANGE THE RESULTS POST-PEER REVIEW, POST-PUBLICATION, IN PLAIN SITE (UNO ET AL.)
- [x] USE THE MOST CONSERVATIVE METHOD FOR MULTIPLE HYPOTHESIS TESTING (BONFERRONI)
- [x] OVERFIT THE MODEL USING REDUNDANT, HIGHLY COLLINEAR VARIABLES
- [x] REMOVE PATIENTS WHO ARE LIKELY TO HAVE ASD FEATURES
- [x] “CORRECT FOR” COVARIATES RELATED TO ASD
- [x] REDUCE SAMPLE SIZE TO REDUCE POWER TO DETECT ASSOCIATION
- [x] CHANGE STUDY DESIGN POST FACTO TO SEE IF ASSOCIATION CAN BE LOST
- [x] FAIL TO REPORT INITIAL ASSOCIATION
- [x] CHANGE CONTINUOUS VARIABLES TO DISCRETE (CUM. EXPOSURE -> “ON TIME” VS. “LATE”


Vaccine
Birth
1 mo
2 mos
4 mos
6 mos
9 mos
12 mos
15 mos
18 mos
19–23 mos
2-3 yrs
4-6 yrs
7-10 yrs
11-12 yrs
13–15 yrs
16–18 yrs
Hepatitis B[1] (HepB)
2 STUDIES SHOW ASSOCIATION
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)
0 STUDIES EXIST
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)
6 STUDIES SHOW ASSOCIATION
Haemophilus influenzae type b[4] (Hib)
2 STUDIES SHOW ASSOCIATION
Pneumococcal conjugate[5] (PCV13)
0 STUDIES EXIST
Inactivated poliovirus[6] (IPV: <18 yrs)
0 STUDIES EXIST
Influenza[7] (IIV; LAIV)
0 STUDIES EXIST
Measles, mumps, rubella[8] (MMR)
2 POSITIVE AND MANY NEGATIVE "STUDIES" EXIST RE: Thompson
Varicella[9] (VAR)
1 STUDY SHOWS ASSOCIATION
Hepatitis A[10] (HepA)
1 STUDY SHOWS ASSOCIATION
Meningococcal[11] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)
0 STUDIES – GBS, PARALYSIS (NUMEROUS)
Tetanus, diphtheria, & acellular pertussis[12] (Tdap: ≥7 yrs)
N/A
Human papillomavirus[13] (2vHPV: females only; 4vHPV, 9vHPV: males and females)
N/A
Meningococcal B[11]
N/A
Pneumococcal polysaccharide[5] (PPSV23)
0 STUDIES
"VACCINES DO NOT CAUSE AUTISM" - CDC

Some Facts About Aluminum:

47%	Oxygen
28%	Silicon
8%	**Aluminum**
5%	Iron
4%	Calcium
3%	Sodium
3%	Potassium
2%	Magnesium

- While abundant in nature, aluminum is not usually biologically available in nature
- >1000 studies show Aluminum is a potent neurotoxin
- Aluminum was grandfathered in to clinical use in vaccines
- First used in vaccines the 1920's
- Present in the form of Aluminum salts (Aluminum hydroxide)
- Interactions between Aluminum and other vaccine excipients are not well studied

Dietary Aluminum

- Most (>99.9%) aluminum in the diet usually is excreted, kept from the blood via intact and properly functioning intestinal tissues
- Bio-available forms of aluminum such as aluminum hydroxide and MF59 are not naturally part of biological exposures in humans and animals
- Lesions in the gut will likely increase dietary aluminum exposures

Population	Year Published	Route of Exposure	NOAEL	LOAEL `	Reference
Mice	1989	Dietary	62 mg Al/kg	155 mg Al/kg	Golub et al 1989
Mice	2001	Dietary	26 mg Al/kg	130 mg Al/kg	Golub et al, 2001
Mice	2005	Dietary	53 mg Al/kg	103 mg Al/kg	Colomina et al, 2005
Mice	2000	Dietary	-	100 mg Al/kg	Golub et al, 2000

Aluminum from Vaccines

- CFR/FDA Safety Levels for an adult is 850 μg per **dose – no body weight**
- Aluminum in parenteral sources (IV) limited to 5 μg/kg/day
- 18 Vaccines in the CDC schedule include Aluminum in various bio-available types
- Babies receive 250 micrograms on the first day of birth in the HepB shot
- 100% of Al from vaccines are absorbed (clearance in days/weeks)
- Only 0.1-0.3% of Al from diet is absorbed

CFR/FDA

- “Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than **4 to 5 [micro]g/kg/day** accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.”

Vaccine Development and Characterization

- Sterility (21 CFR 610.12)
- General Safety (21 CFR 610.11)
  - test on final container product
  - detection of extraneous toxic contaminants
- Purity (21 CFR 610.13)
  - pyrogenicity
  - moisture content
- Identity (21 CFR 610.14)
  - on final container, e.g. SDS-PAGE, Western blot,
- Other release tests
  - in process testing critical for safety and manufacturing consistency

21 CFR 610.15: Constituent Materials.

- (a) *Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality.

- Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient…

21 CFR 610.15: Constituent materials.

- An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product.

- The amount of aluminum in the recommended individual dose of a biological product shall not exceed:
  - (1) 0.85 milligrams if determined by assay;
  - (2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or
  - (3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe…

Question: How did CFR/FDA Come to a Vaccine MSL 850 mcg/AL per DOSE, with no reference to body weight?

- MRL - MINIMAL RISK LEVELS
- NOAEL - no-observed-adverse-effect-level
- LOAEL - lowest-observed-adverse-effect level

ELSEVIER

Vaccine 20 (2002) S13–S17

Vaccine

www.elsevier.com/locate/vaccine

Aluminum toxicokinetics regarding infant diet and vaccinations

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Received 4 June 2001; accepted 7 August 2001

Abstract

Some vaccines contain aluminum adjuvants to enhance the immunological response, and it has been postulated that this aluminum could contribute to adverse health effects, especially in children who receive a vaccination series starting at birth. The pharmacokinetic properties and end-point toxicities of aluminum are presented. In assessing the relevance of dietary and medical aluminum exposure to public health, we estimated infant body burdens during the first year of life for breast milk and formula diets and for a standard vaccination schedule. We then compared those body burdens with that expected for intake at a level considered safe for intermediate-duration exposure. The methodology blends intake values and uptake fractions with an aluminum retention function derived from a human injection study using radioactive ^{26}Al. The calculated body burden of aluminum from vaccinations exceeds that from dietary sources, however, it is below the minimal risk level equivalent curve after the brief period following injection. Published by Elsevier Science Ltd.

Keywords: Aluminum; Vaccine; Diet

1. Introduction

Keith et al.

- analyzed the pharmacokinetics of aluminum for infant dietary and vaccine exposures
- compared the resulting body burdens to those based on the minimal risk levels (MRLs) established by the Agency for Toxic Substances and Disease Registry (ATSDR)

concentration gives the daily aluminum intake through 6 months of age. During the second 6 months, introduction of semisolid food increases the aluminum intake to an average 0.7 mg per day [21]. An estimate of infant aluminum body burden during year 1 was developed using a 0.78% uptake factor and applying the Priest et al. [11] retention function

vated serum aluminum levels, a condition that is now known to be preventable by using water with low aluminum content. Other more subtle neurological effects that have been induced in animal models or associated with human occupational exposure include memory loss, fatigue, depression, behavioral modifications, and learning impairment.

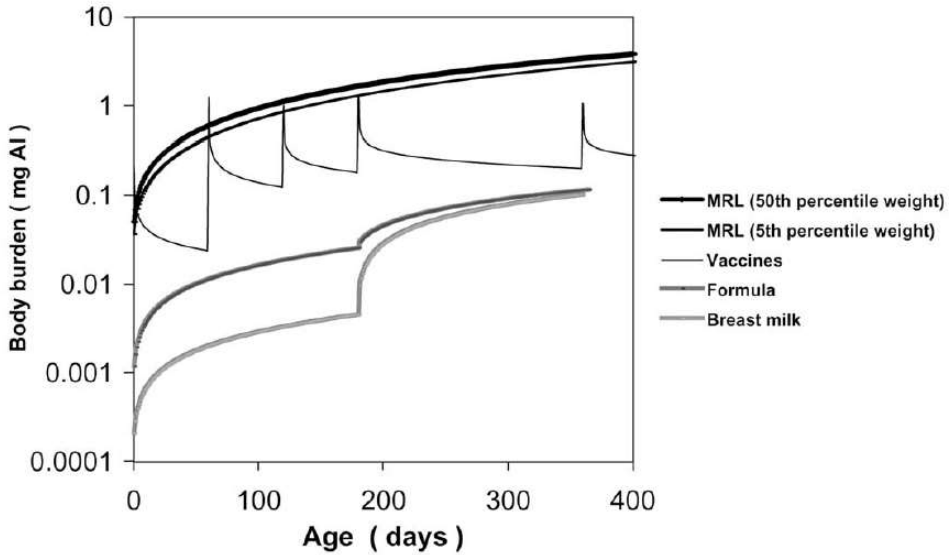
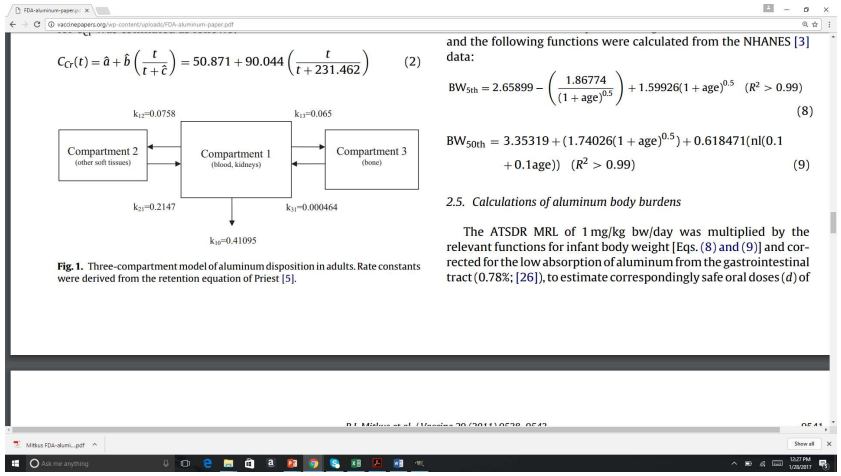


Fig. 1. Aluminum body burden contributions from diet and vaccines relative to MRL level intake.

Mitkus et al



$$C_{Cr}(t) = \hat{a} + \hat{b}\left(\frac{t}{t+\hat{c}}\right) = 50.871 + 90.044\left(\frac{t}{t+231.462}\right) \quad (2)$$

Fig. 1. Three-compartment model of aluminum disposition in adults. Rate constants were derived from the retention equation of Priest [5].

and the following functions were calculated from the NHANES [3] data:

$$BW_{5th} = 2.65899 - \left(\frac{1.86774}{(1+age)^{0.5}}\right) + 1.59926(1+age)^{0.5} \quad (R^2 > 0.99) \quad (8)$$

$$BW_{50th} = 3.35319 + (1.74026(1+age)^{0.5}) + 0.618471(nl(0.1 + 0.1age)) \quad (R^2 > 0.99) \quad (9)$$

2.5. Calculations of aluminum body burdens

The ATSDR MRL of 1 mg/kg bw/day was multiplied by the relevant functions for infant body weight [Eqs. (8) and (9)] and corrected for the low absorption of aluminum from the gastrointestinal tract (0.78%; [26]), to estimate correspondingly safe oral doses (d) of

- Updated the analysis of Keith et al.
- (then) current pediatric vaccination schedule, baseline aluminum levels at birth
- Adjusted the analysis using
  - an aluminum retention function that reflects changing glomerular filtration rates in infants
  - an adjustment for the kinetics of aluminum efflux at the site of injection
  - contemporaneous MRLs
  - the most recent infant body weight data for children 0–60 months of age

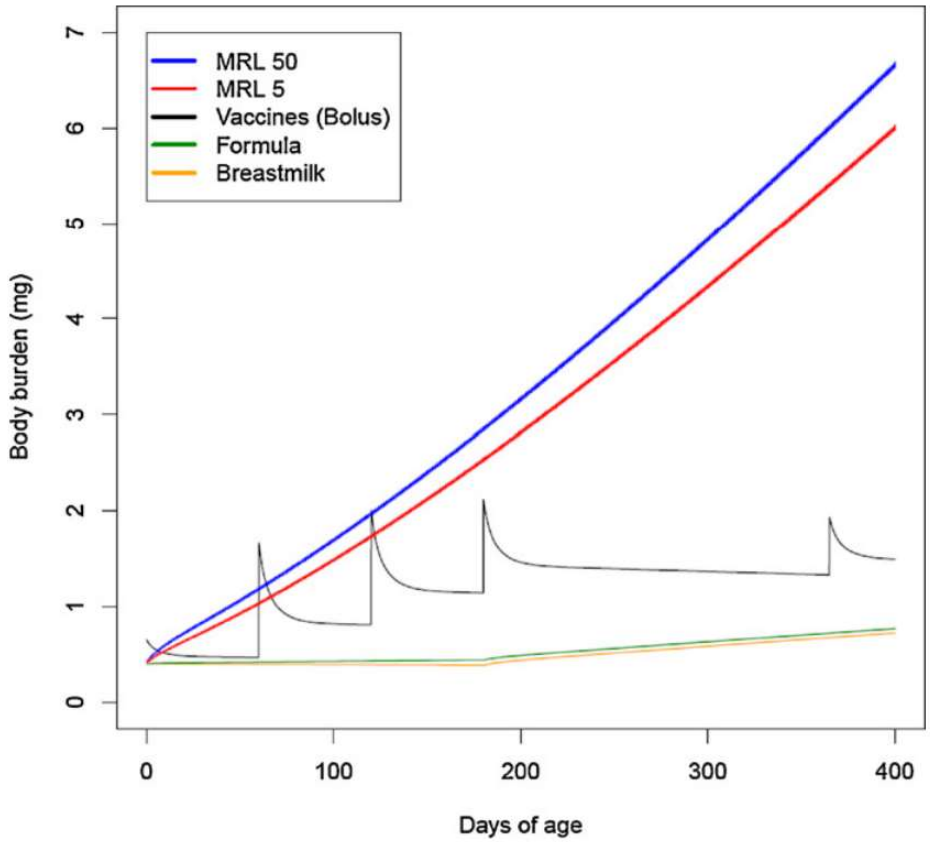


Fig. 2. Aluminum body burden contributions from diet and vaccines (100%, instantaneous absorption assumed) relative to current MRL level intake in infants. *Note*: the body burden of aluminum is greater than zero at birth, since infants are exposed

The determinations of the kinetics of aluminum retention by Priest [21,5] were based on experiments where human volunteers were given an intravenous injection of aluminum citrate. For vaccines, the injection is intramuscular, the aluminum is in an insoluble form (e.g., as the phosphate or hydroxide of aluminum), and muscle at the site of injection is considered to be a storage depot for aluminum. Over time the insoluble aluminum hydroxide or aluminum phosphate particles are solubilized by citrate ions in the interstitial fluids of muscle. After solubilization, the uptake and distribution kinetics of aluminum will likely be similar to the kinetics determined by the human volunteer studies. However, it is unlikely that the process of absorption from the site of intramuscular injection into the blood is instantaneous, as is assumed for intravenous exposures and as presumed by the retention functions used to generate Fig. 2 and by Keith et al. [1].

Flarend et al. [27] investigated the absorption into the blood of aluminum hydroxide and aluminum phosphate following intramuscular injection into New Zealand White rabbits. Two important observations were made in their experiments: (1) only a fraction of the injected aluminum was taken up from the site of injection into blood over the 28-day experimental period, and (2) absorption of neither adjuvant was instantaneous. Specifically, blood concentrations of aluminum hydroxide decreased to a minimum by the end of the experiment (reached a terminal phase), where as aluminum phosphate blood concentrations were relatively constant

Disagreement Between Two Committees

Joint Expert Committee on Food Additives (FAO/WHO; 1989, 2011)

- 1989. Provisional Tolerable Weekly Intake (PTWI) established at 1 mg/kg all dietary sources and additives. Mean highest daily intake US children 0.5 mg Al/kg per day[1]
- 2011. Previous PTWI of 1 mg Al/kg withdrawn. Revised PTWI to 2 mg/kg (adults)[2]

Agency for Toxic Substances and Disease Registry (ATSDR) CAS ID #: 7429-90-5 2008

- 2008 (CAS ID #: 7429-90-5)[3]
- Daily dietary intake of Al 2 mg/kg-day in adults
- Minimal Risk Level (MRL) 1 mg/kg-day (adults) same as No Observed Adverse Effect Level (NOAEL)

[1]Evaluation of certain food additives and contaminants [Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 776, 1989
[2] Evaluation of certain food additives and contaminants (Seventy fourth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, JECFA/74/SC, 2011
[3]Agency for Toxic Substances and Disease Registry (ATSDR) CAS ID #: 7429-90-5

ANIMAL STUDIES OF DOSE-RELATED ALUMINUM TOXICITY (DIETARY)

Source/Dose	Animal(age)	Adverse Event(s)
ORAL		
rats (adults)	230 mg Al/kg/day	erythropoiesis
rats (adults)	230 mg/kg/day	erythrocyte damage
mouse (dams)	230 mg/kg/day	increased susc. Infection
rats (pups)	**54 mg/kg**	**delay in maturation**
rats/mice (pups)	104 mg/kg/day	decrease in bw gain

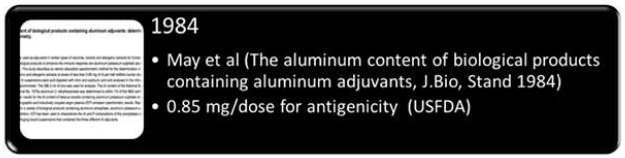
Rats: Adult weight Males 300-500g, Females 250-300g Birth weight 5-6g
Mice: Adult weight Males 20-30 g, Females 18-35g Birth weight 1-2 g

How did 1 mg Al/kg/week become 1 mg/kg/day and 850 mcg *per dose regardless of body weight*

- 1981-CFR amended to include 1250 μg/dose
- 1996-2007 PTWI estimated at **1 mg/kg/week**; 0.5 mg/kg-day US child > 2 years of age (WHO Evaluation and Certain Food Additives and Contaminants. Section 4.1 Aluminum, 1996-2007)
- 1996 **Committee on Nutrition** Aluminum Neurotoxicity in Infants and Children (J Pediatrics),

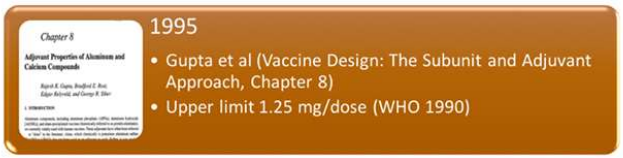
"1" mg/kg-day (in error as to PTWI- "provisional tolerable intake")

- **2001 850 μg "selected empirically from data because it enhances the antigenicity and effectiveness of the vaccine" (Baylor et al 2001)**
- 2001-2008 ATSDR set MRL/NOAEL to 1 mg/kg/**day** from all sources based on Golub 26 mg/kg-day NOAEL (ATSDR references Baylor et al (2001),
- 2001 MRL/NOAEL 2 mg/kg-day in adult humans from dietary sources (Golub et al 2001; 62 mg/kg-day, Keith et al)
- 2011 MRL=1 mg/kg bw/**day** (ATSDR, 2008), Mitkus (2011)
- 2017: CFR is 850 μg/DOSE.



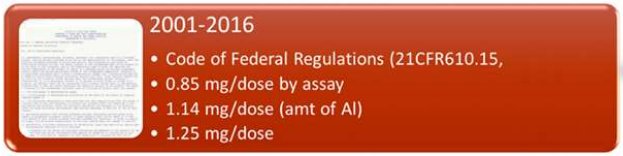
1984

- May et al (The aluminum content of biological products containing aluminum adjuvants, J.Bio, Stand 1984)
- 0.85 mg/dose for antigenicity (USFDA)



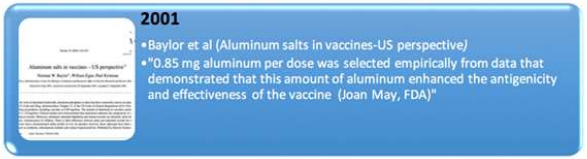
1995

- Gupta et al (Vaccine Design: The Subunit and Adjuvant Approach, Chapter 8)
- Upper limit 1.25 mg/dose (WHO 1990)



2001-2016

- Code of Federal Regulations (21CFR610.15,
- 0.85 mg/dose by assay
- 1.14 mg/dose (amt of Al)
- 1.25 mg/dose

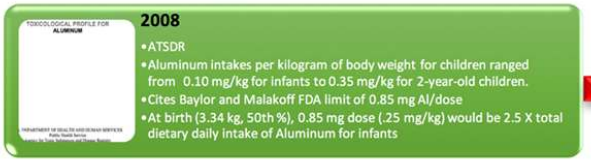


2001

- Baylor et al (Aluminum salts in vaccines-US perspective)
- "0.85 mg aluminum per dose was selected empirically from data that demonstrated that this amount of aluminum enhanced the antigenicity and effectiveness of the vaccine (Joan May, FDA)"

2000

- Malakoff (Aluminum is Put on Trial as a Vaccine Booster, Science 2000 May 26)
- "Regulatory and manufacturing requirements, for instance, would make it "a nightmare" to create different formulas for an initial vaccine and its booster, says Nathalie Garcon-Johnson of SmithKline Beecham Biologicals"

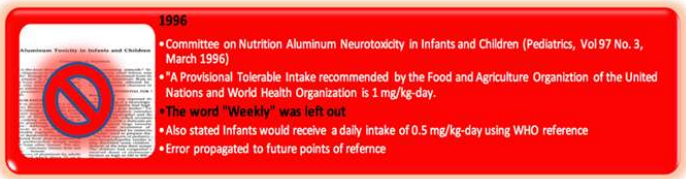


2008

- ATSDR
- Aluminum intakes per kilogram of body weight for children ranged from 0.10 mg/kg for infants to 0.35 mg/kg for 2-year-old children.
- Cites Baylor and Malakoff FDA limit of 0.85 mg Al/dose
- At birth (3.34 kg, 50th %), 0.85 mg dose (.25 mg/kg) would be 2.5 X total dietary daily intake of Aluminum for infants

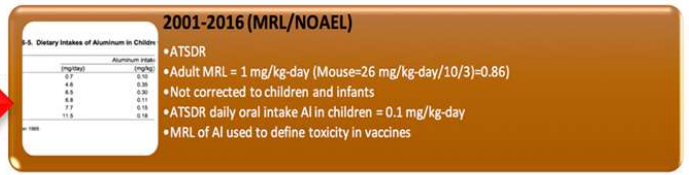
1996-2007

- Evaluation Of Certain Food Additives and Contaminants (World Heath Organization, Sec. 4.1 Aluminum)
- Mean exposure to US children =0.5 mg/kg-day
- Health-based guidance as Provisional Tolerable Weekly Intake (PTWI) = 1.0 mg/kg per week in Adults
- The calculated daily intake is 0.14 mg/kg-day
- ATSDR daily intake = 0.1 mg/kg-day in children.
- The NOAEL (mg/kg-day) = 0.1-0.14 mg Al/kg-day



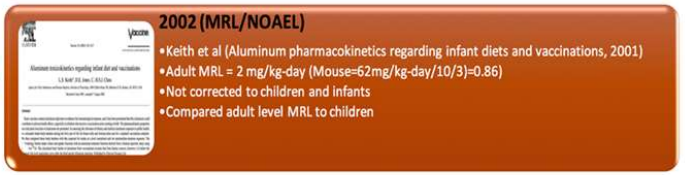
1996

- Committee on Nutrition Aluminum Neurotoxicity in Infants and Children (Pediatrics, Vol 97 No. 3, March 1996)
- "A Provisional Tolerable Intake recommended by the Food and Agriculture Organiztion of the United Nations and World Health Organization is 1 mg/kg-day.
- **The word "Weekly" was left out**
- Also stated Infants would receive a daily intake of 0.5 mg/kg-day using WHO reference
- Error propagated to future points of refernce



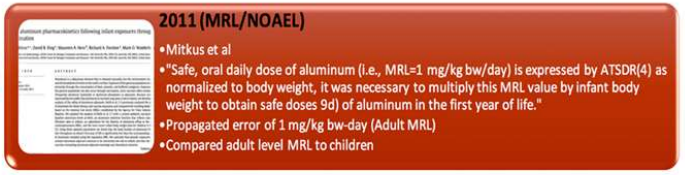
2001-2016 (MRL/NOAEL)

- ATSDR
- Adult MRL = 1 mg/kg-day (Mouse=26 mg/kg-day/10/3)=0.86)
- Not corrected to children and infants
- ATSDR daily oral intake Al in children = 0.1 mg/kg-day
- MRL of Al used to define toxicity in vaccines



2002 (MRL/NOAEL)

- Keith et al (Aluminum pharmacokinetics regarding infant diets and vaccinations, 2001)
- Adult MRL = 2 mg/kg-day (Mouse=62mg/kg-day/10/3)=0.86)
- Not corrected to children and infants
- Compared adult level MRL to children



2011 (MRL/NOAEL)

- Mitkus et al
- "Safe, oral daily dose of aluminum (i.e., MRL=1 mg/kg bw/day) is expressed by ATSDR(4) as normalized to body weight, it was necessary to multiply this MRL value by infant body weight to obtain safe doses 9d) of aluminum in the first year of life."
- Propagated error of 1 mg/kg bw-day (Adult MRL)
- Compared adult level MRL to children

Birth to 15 Months	(Adapted from "CDC Vaccine Schedules 2016")																
Vaccine	Aluminum Content (ug)* per dose	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16-18 yrs
Hepatitis B1 (HepB)	250	1st dose		2nd dose		3rd dose											
Rotavirus2 (RV)				1st dose	2nd dose												
RV1 (2-dose series); RV5 (3-dose series)																	
Diphtheria, tetanus, & acellular pertussis3 (DTaP: <7 yrs)	625			1st dose	2nd dose	3rd dose				←4th dose→			5th dose				
Haemophilus influenzae type b4 (Hib)	225			1st dose	2nd dose			←3rd or 4th dose,									
Pneumococcal conjugate5 (PCV13)	125			1st dose	2nd dose	3rd dose		←4th dose→									
Inactivated poliovirus6 (IPV:<18 yrs)				1st dose	2nd dose	←3rd dose→							←4th dose→				
Influenza7 (IIV; LAIV)						Annual vaccination (IIV only) 1 or 2 doses				Annual vaccination (IIV only) 1 or 2 doses		Annual vaccination (IIV only) 1 or 2 doses			Annual vaccination (IIV only) 1 or 2 doses		
Measles, mumps, rubella8 (MMR)							1st dose						2nd dose				
Varicella9 (VAR)								1st dose					2nd dose				
Hepatitis A10 (HepA)	250							1st dose		2nd dose							
Meningococcal11 (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)															1st dose		
Tetanus, diphtheria, & acellular pertussis12 (Tdap: ≥7 yrs)															(Tdap)		
Human papillomavirus13 (2vHPV:females only; 4vHPV, 9vHPV:males and females)															(3 dose series)		
Meningococcal B11																	
Pneumococcal polysaccharide5 (PPSV23)																	
	* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875							

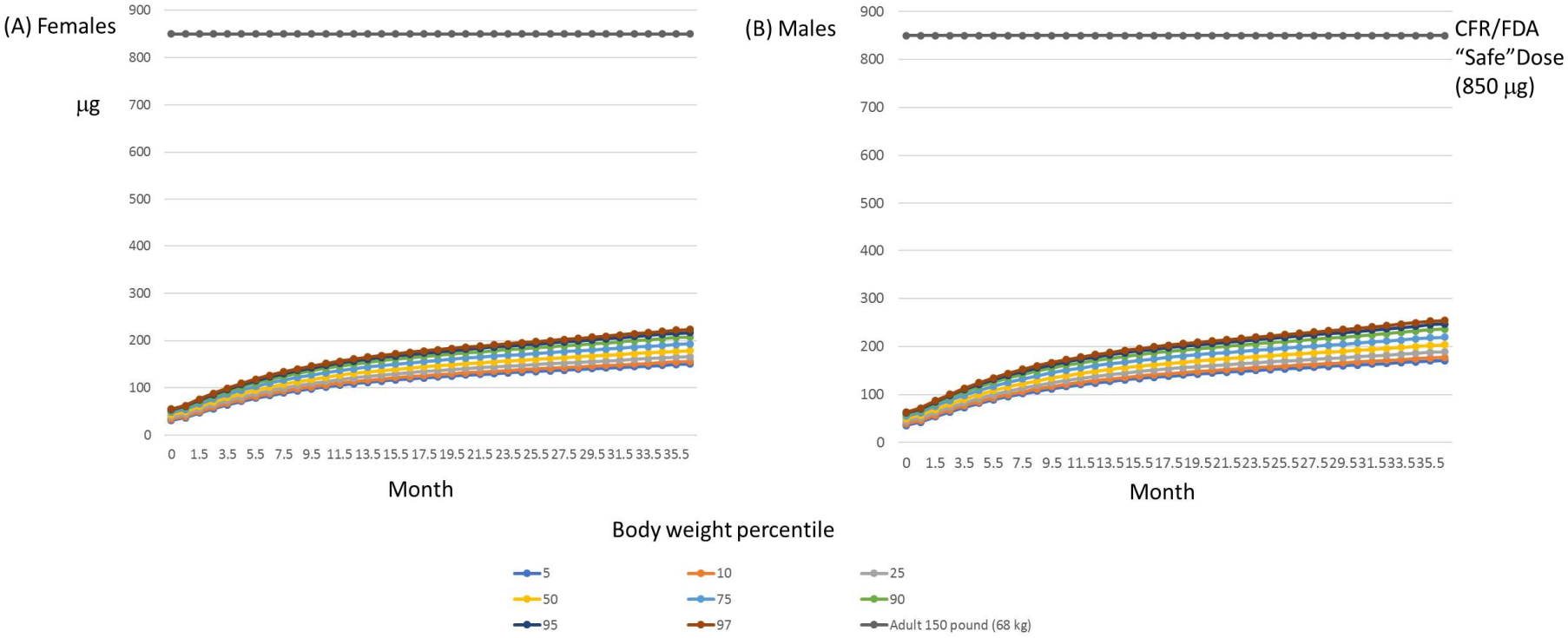
Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B[1] (HepB)	2 STUDIES SHOW ASSOCIATION															
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			0 STUDIES EXIST													
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			6 STUDIES SHOW ASSOCIATION													
Haemophilus influenzae type b[4] (Hib)			2 STUDIES SHOW ASSOCIATION													
Pneumococcal conjugate[5] (PCV13)			0 STUDIES EXIST													
Inactivated poliovirus[6] (IPV: <18 yrs)			0 STUDIES EXIST													
Influenza[7] (IIV; LAIV)					0 STUDIES EXIST											
Measles, mumps, rubella[8] (MMR)					2 POSITIVE AND MANY NEGATIVE "STUDIES" EXIST RE: Thompson											
Varicella[9] (VAR)							1 STUDY SHOWS ASSOCIATION									
Hepatitis A[10] (HepA)							1 STUDY SHOWS ASSOCIATION									
Meningococcal[11] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)			0 STUDIES – GBS, PARALYSIS (NUMEROUS)													
Tetanus, diphtheria, & acellular pertussis[12] (Tdap: ≥7 yrs)													N/A			
Human papillomavirus[13] (2vHPV: females only; 4vHPV, 9vHPV: males and females)														N/A		
Meningococcal B[11]														N/A		
Pneumococcal polysaccharide[5] (PPSV23)											0 STUDIES					

"VACCINES DO NOT CAUSE AUTISM" - CDC

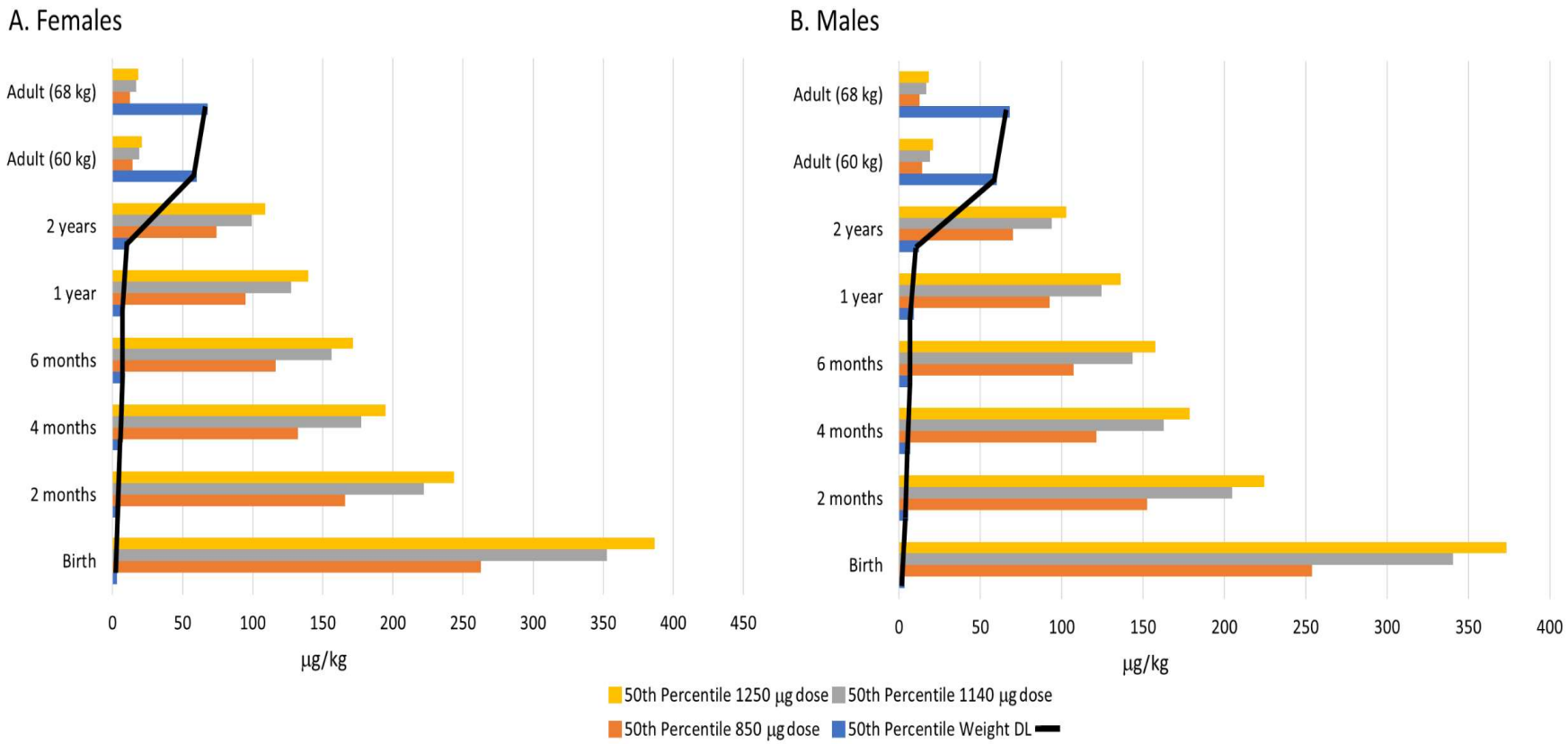
* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875								

Vaccine	Aluminum Content (ug)* per dose	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16-18 yrs
Hepatitis B1 (HepB)	250	1st dose		2nd dose		3rd dose											
Rotavirus2 (RV)				1st dose	2nd dose												
RV1 (2-dose series); RV5 (3-dose series)																	
Diphtheria, tetanus, & acellular pertussis3 (DTaP: <7 yrs)	625			1st dose	2nd dose	3rd dose				←4th dose→			5th dose				
Haemophilus influenzae type b4 (Hib)	225			1st dose	2nd dose			←3rd or 4th dose,									
Pneumococcal conjugate5 (PCV13)	125			1st dose	2nd dose	3rd dose		←4th dose→									
Inactivated poliovirus6 (IPV:<18 yrs)				1st dose	2nd dose	←3rd dose→							←4th dose→				
Influenza7 (IIV; LAIV)						Annual vaccination (IIV only) 1 or 2 doses				Annual vaccination (IIV only) 1 or 2 doses		Annual vaccination (IIV only) 1 or 2 doses			Annual vaccination (IIV only) 1 or 2 doses		
Measles, mumps, rubella8 (MMR)							1st dose						2nd dose				
Varicella9 (VAR)								1st dose					2nd dose				
Hepatitis A10 (HepA)	250							1st dose		2nd dose							
Meningococcal11 (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)															1st dose		
Tetanus, diphtheria, & acellular pertussis12 (Tdap: ≥7 yrs)															(Tdap)		
Human papillomavirus13 (2vHPV:females only; 4vHPV, 9vHPV:males and females)															(3 dose series)		
Meningococcal B11																	
Pneumococcal polysaccharide5 (PPSV23)																	
	* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875							

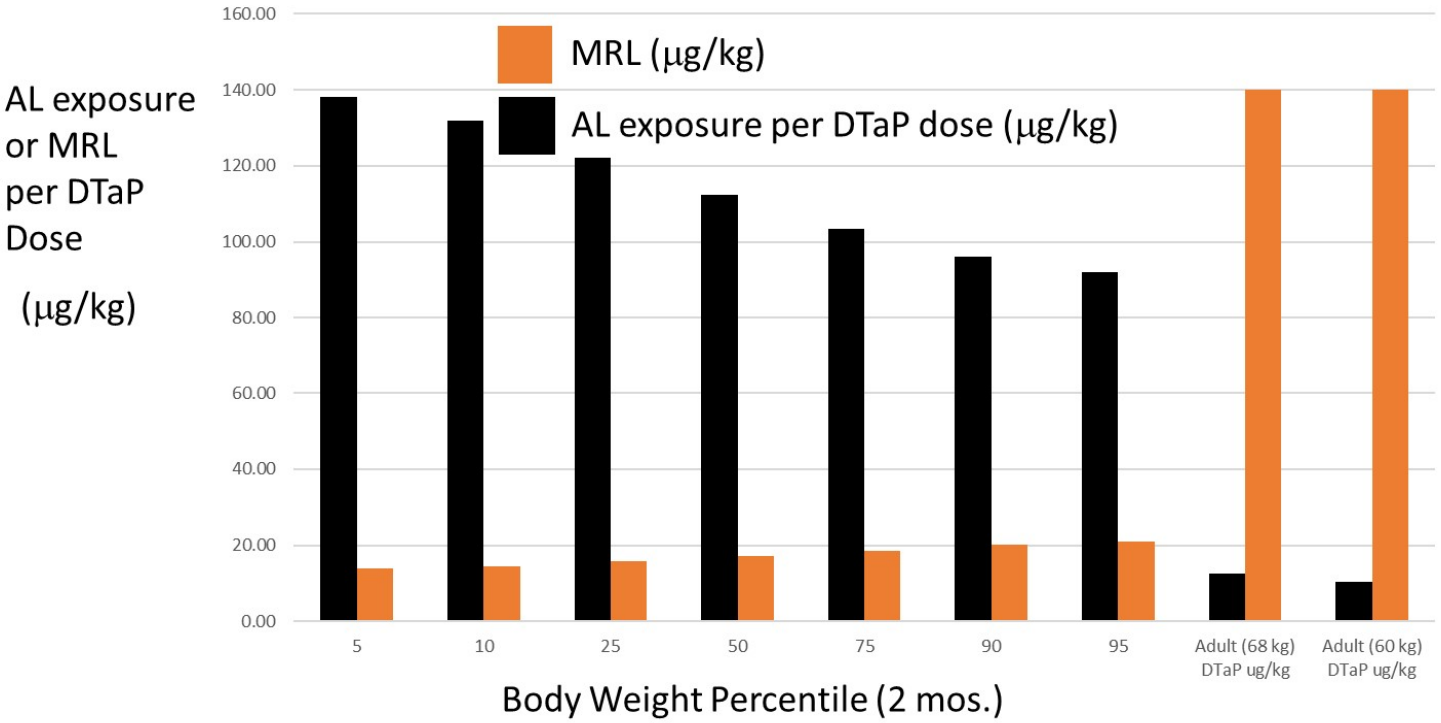
BW Corrected AL CFR/FDA Limits (Clark's Rule)



BW-Informed FDA Dose Limits and Vaccine Exposures, Expressed as μg/kg, Birth through Adulthood

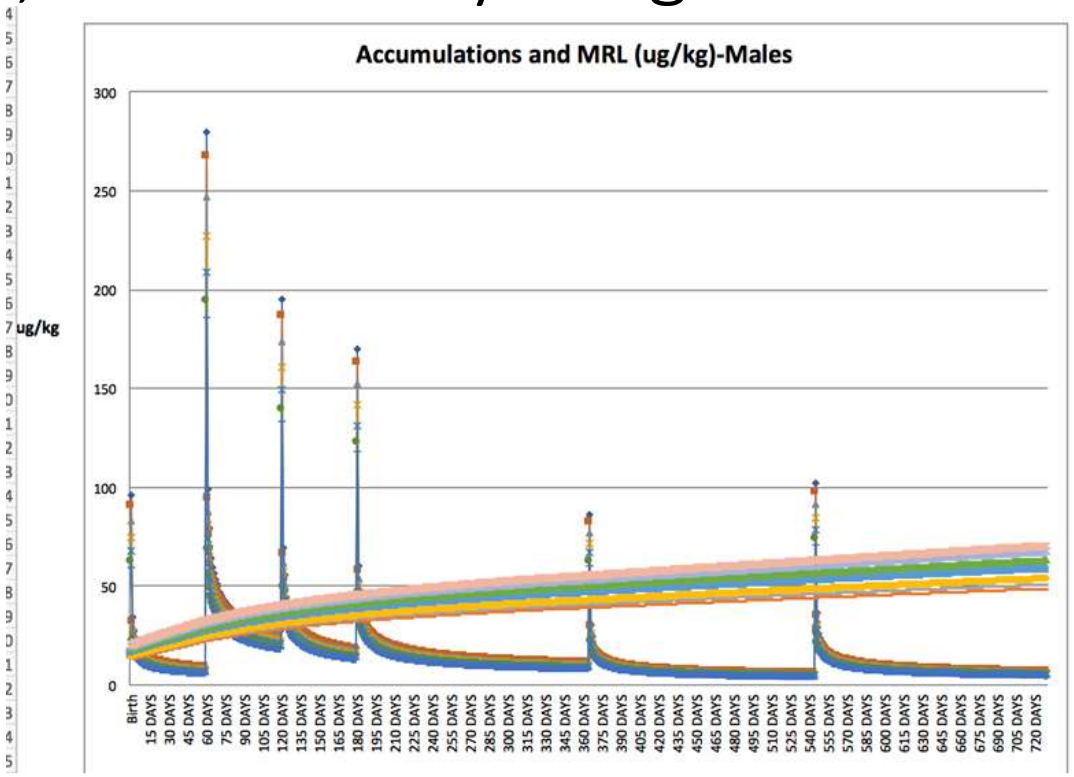


Calculated Pediatric MRL and the AL Exposures from DTaP Vaccine for Children (and Adults) using Clark's Rule to Accommodate Pediatric Body Weights (μg/kg, 2 months and Adult).



US Vaccine Aluminum Dose Accumulation and Pediatric Dose Limits (μg/kg IPAK 2017) Males, 50thtile body weight

μg/kg



Day

"So the level of aluminum in vaccines, however, is **trivial**. And you frankly **ingest much more** aluminum from either in the water that you drink, or anything made from water on this planet, and many of the foods that we eat contain quantities of aluminum **far greater** than you're ever going **to get** in vaccines."

	Aluminum intake	
Age-sex group	(mg/day)	(mg/kg)
6–11-Months	0.7	0.10
2-Years	4.6	0.35
6-Years	6.5	0.30
10-Years	6.8	0.11
14–16-Years (females)	7.7	0.15
14–16-Years (males)	11.5	0.18

Source: Pennington and Schoen 1995

Pediatric Dietary Aluminum

Age	Aluminum intake (mg/day)	Aluminum intake (mg/kg-day)
6 months – 1 year	0.7	0.10
2 years	4.6	0.35
6 years	6.5	0.30
10 years	6.8	0.11

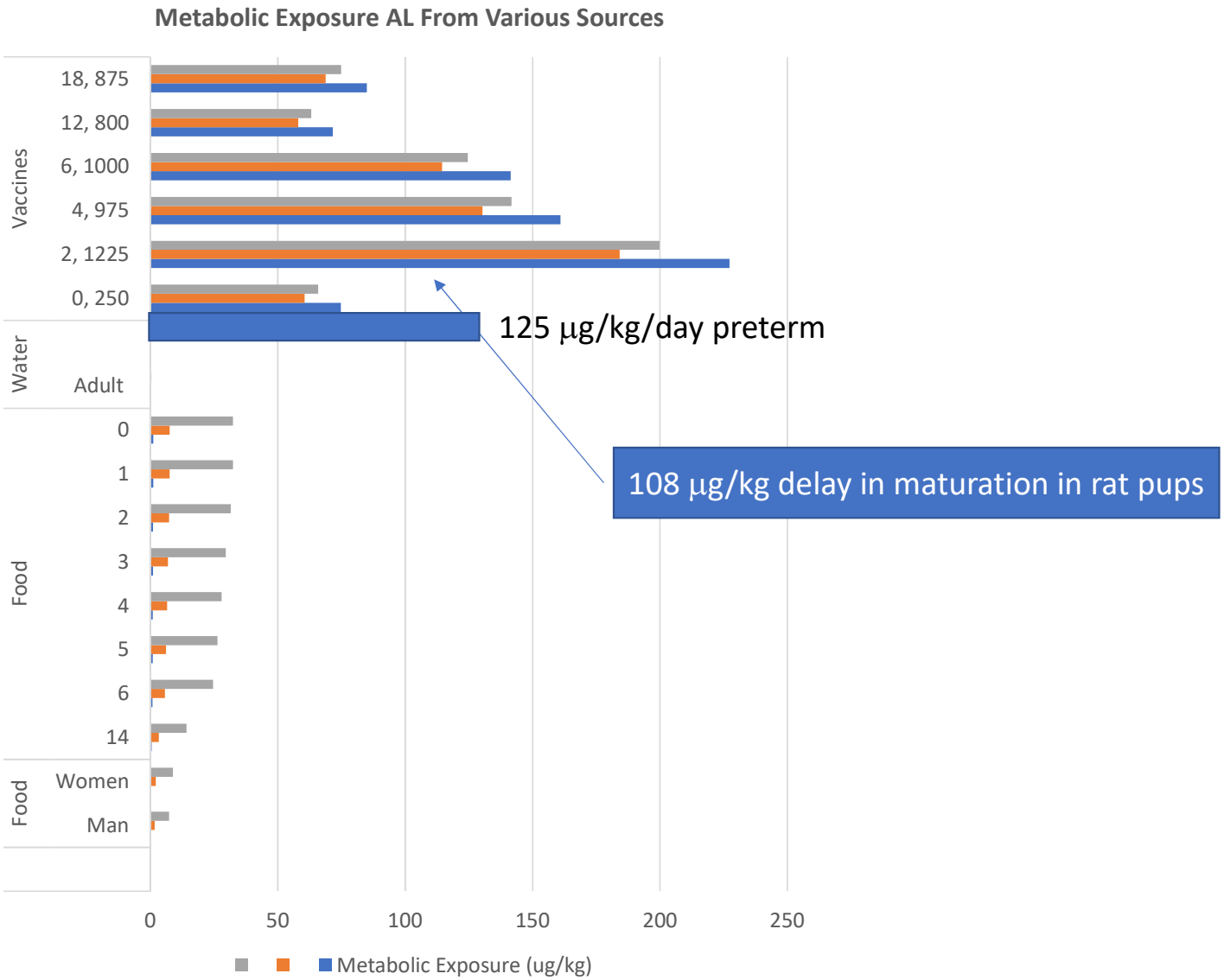
Pennington JA, Schoen SA. 1995. Estimates of dietary exposure to aluminium. Food Addit Contam. 12(1):119-28. PubMed PMID: 7758626.

Source	Al concentration	Daily Al exposure	Estimated percentage absorbed	Al absorbed daily (µg/kg)[a]
Typical Exposures				
Water	Average ~ 70 µg/l	100 µg	0.3 [b]	0.004
Food - total diet		3500-10,000 µg [c]	0.1 to 0.3 [d]	0.05-0.4
Air-office	0.15 µg/m³ [e]	1 µg	1 to 2 from lungs [f] 0.1 to 0.3 from GI tract	0.0002 0.00003
Air-outside	0.2 - 1 µg/m³ [e,g]	4 µg [h]	1 to 2 from lungs [f] 0.1 to 0.3 from GI tract	0.001 0.0001
Antiperspirants	5-7.5% [i]	50,000-75,000 µg	up to 0.012 [j]	up to 0.1
Vaccines, pediatric patient	125-330 µg/dose	1.4 µg [k]	100 eventually [l]	0.07
Elevated Exposures				
Antacids/phosphate Binders		up to 5,000,000 µg	0.1	80
Industrial Air	25-2500 µg/m³	250-25,000 µg per work day	1 to 2 from lungs [f] 0.1 to 0.3 from GI tract	0.6-8 0.008-1
Allergy immunotherapy	150-850 µg/dose	7-40 µg [m]	100 eventually [l]	0.1-0.6
Dialysis solution	If tap water 50 µg/l	2400 µg	25 [n]	9
Total Parenteral Nutrition Solutions	Neonatal/pediatric	9-23 µg/kg [o]	100	9-23
	Adult	1.5 µg/kg [p]	100	1.5

Age-Sex group	Dietary Aluminum intake		Metabolically available (mcg Al/kg)		Vaccine (by schedule)	%Vaccine	% increase
	(mg Al/day)	mcg Al/kg	Diet (mcg Al/kg)	Vaccines (mcg Al/kg)			
Birth	0.1	29	2.9	74.7	(HepB)	96%	**2676%**
6-11 Months	0.7	100	10	141.1	(DTaP, HepB, HiB, PCV)	93%	**1411%**
2-Years	4.6	350	35	5.7	(DTaP 18 month-remaining)	14%	16%
6-Years	6.5	300	30	28.4	(Tdap)	49%	95%
10-Years	6.8	110	11	40.3	en,Tdap, HPV)-Age 11-12 yrs)	79%	366%
14-16-Years (females-48 kg)	7.7	150	15	10.4	(HPV-2nd dose)	41%	69%
14-16-Years (males-50 kg)	11.5	180	18	10	(HPV-2nd dose)	36%	56%

Birth	Dorea et al, 2015
6 mo-16yr	Pennington and Schoen, 1995

0.1% absorbed (Yokel)


Metabolic Exposure AL From Various Sources
Vaccines
18, 875
12, 800
6, 1000
4, 975
2, 1225
0, 250
Water
Adult
Food
0
1
2
3
4
5
6
14
Food
Women
Man
125 µg/kg/day preterm
108 µg/kg delay in maturation in rat pups
0
50
100
150
200
250
Metabolic Exposure (ug/kg)

Updated Maxims in Toxicology

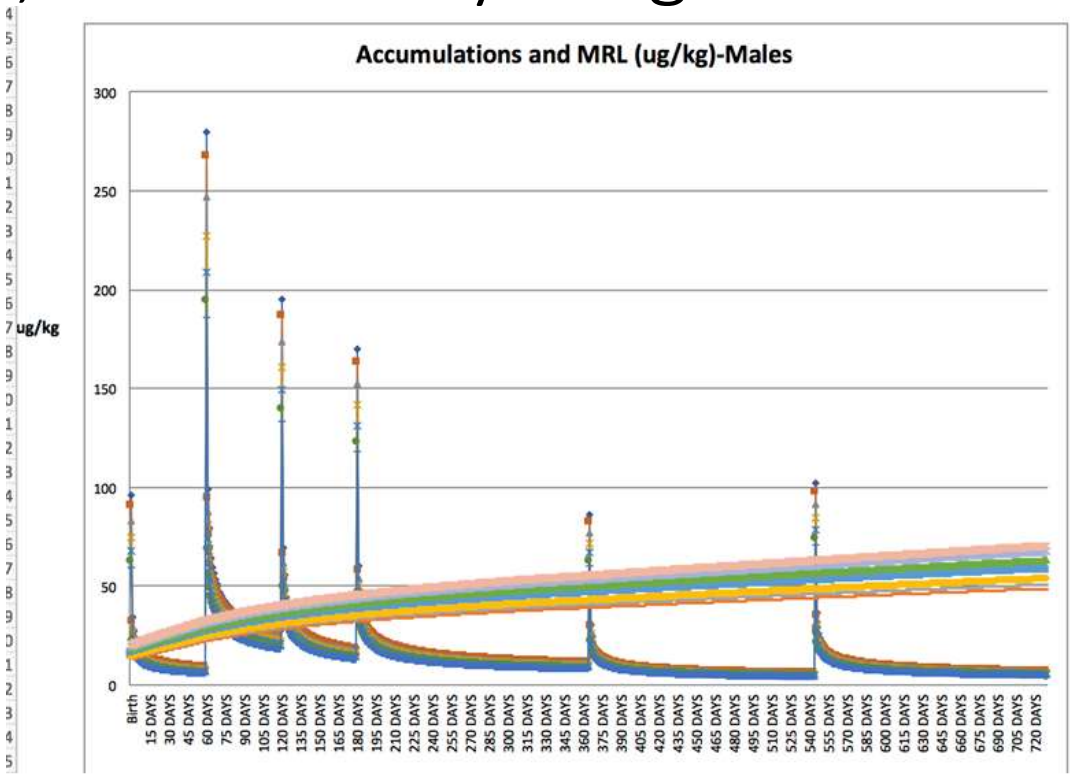
- **“The dose makes the poison.”** – Paracelsus, 1538

- **“Body weight makes the dose makes the poison.”** – JLW, 2017

[*Alle Dinge sind Gift und nichts ist ohne Gift, allein die Dosis macht es, dass ein Ding kein Gift ist*. All things are poison and nothing is without poison, only the dosage makes a thing not poison "Die dritte Defension wegen des Schreibens der neuen Rezepte," Septem Defensiones 1538. Werke Bd. 2, Darmstadt 1965, p. 510

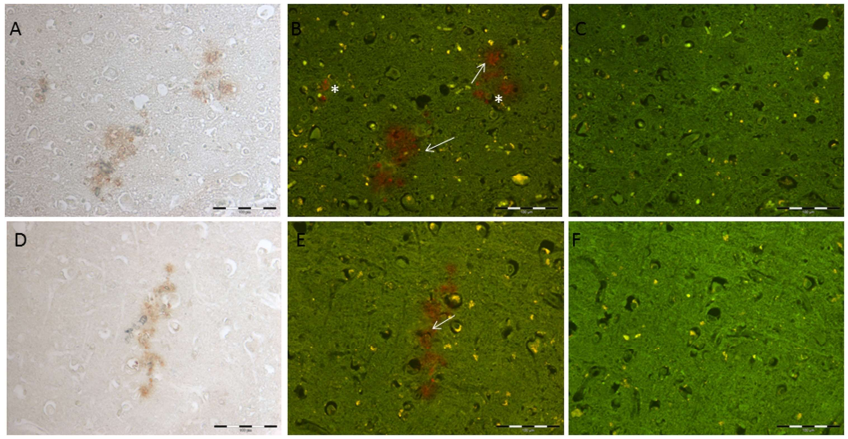
US Vaccine Aluminum Dose Accumulation and Pediatric Dose Limits (μg/kg IPAK 2017) Males, 50thtile body weight

μg/kg



Day

***Intensity**
***Repeatedness**
***Duration of Exposure Matters**



cortext

parietal cortex

Journal of Trace Elements in Medicine and Biology
Volume 40, March 2017, Pages 30–36
ELSEVIER

Toxicology

Aluminium in brain tissue in familial Alzheimer's disease

Ambreen Mirza[a], Andrew King[b,c], Claire Troakes[c], Christopher Exley[a]
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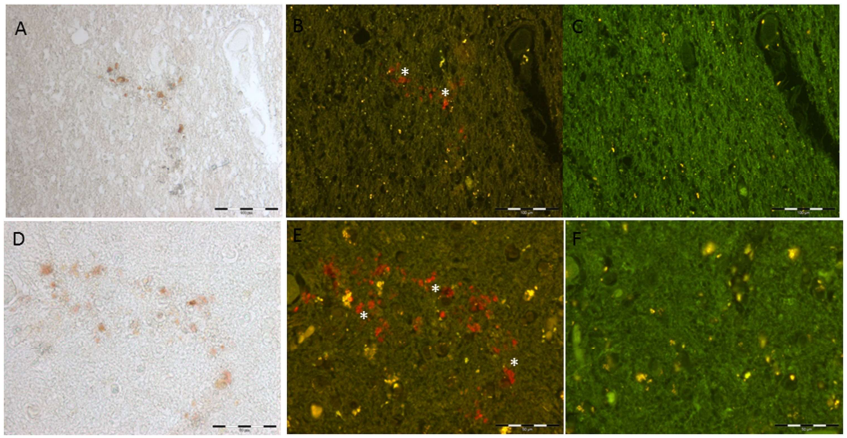
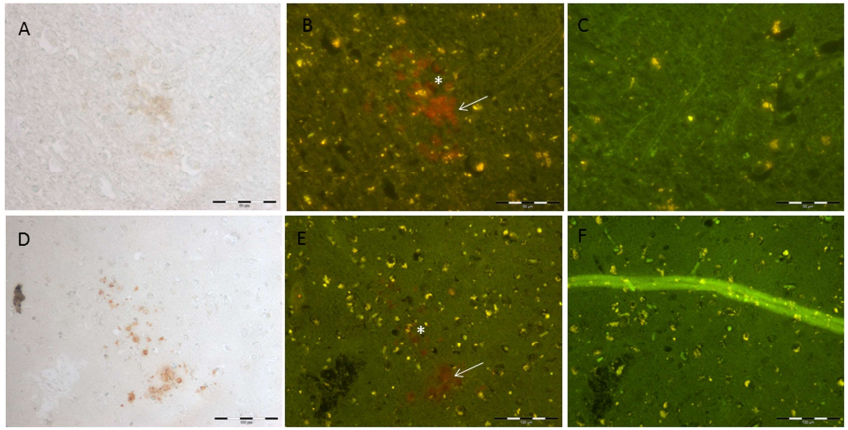
http://dx.doi.org/10.1016/j.jtemb.2016.12.001

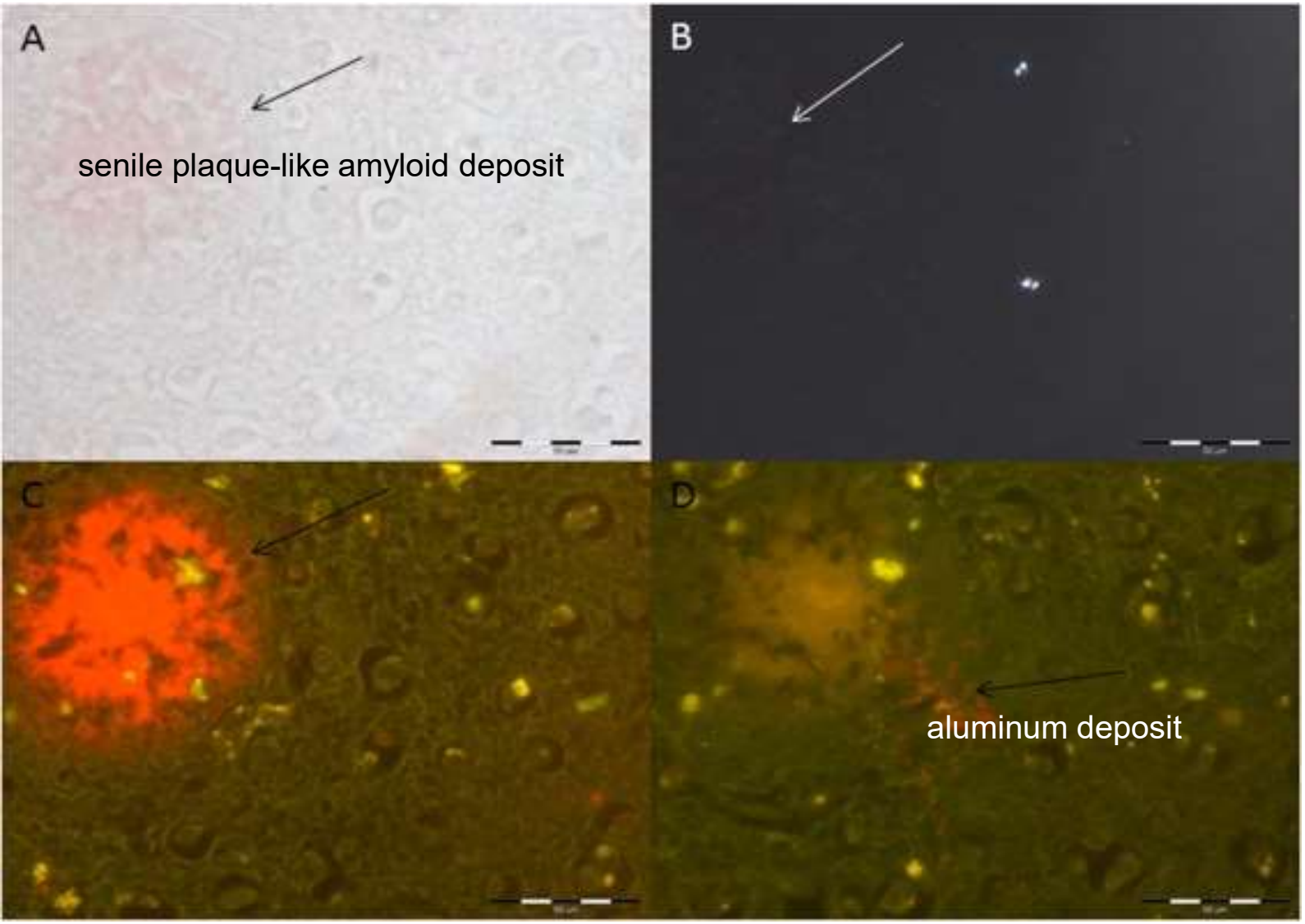
Abstract

... a diagnosis of familial Alzheimer's disease





neocortex



Ambreen Mirza, Andrew King, Claire Troakes, Christopher Exley Journal of Trace Elements in Medicine and Biology, Volume 40, 2017, 30–36

www.cnn.com/2017/02/15/health/thimerosal-vaccine-preservative-explainer/

CNN Health » Diet + Fitness | Living Well | Parenting + Family — Live TV — U.S. Edition +

Thimerosal: Everything you need to know about this vaccine preservative

By Jen Christensen, CNN
Updated 7:52 AM ET, Wed February 15, 2017

Source: CNN

NIH doctor debunks celebrities on vaccines 04:36

Top stories

38-year-old kidnapping of Etan Patz solved

House panel investigates handling of info at Mar-a-Lago

Mortgage Payment Calculator

Loan amount $225,000

Loan type 15-Year Fixed

APR 3.20%

CDC A-Z INDEX

The science is clear: Vaccines are safe, effective, and do not cause autism

Johns Hopkins public health expert Daniel Salmon discusses vaccine safety and the potential hazards pose by fewer children being vaccinated

Childhood vaccines are safe. Seriously.

By Jen Christensen and Nadia Kounang, CNN
Updated 3:18 PM ET, Tue July 1, 2014

Source: CNN

Should I get my child vaccinated? 01:14

Top stories

Tapper to Trump: Media didn't fire Flynn, you did

Little Caesars founder quietly paid Rosa Parks' rent for years

Story highlights

Review of more than 20,000 scientific titles and 67 papers finds no evidence linking vaccines, autism

Children should get vaccinated against preventable and potentially deadly diseases. Period.

That's what a project that screened more than 20,000 scientific titles and 67 papers on vaccine safety

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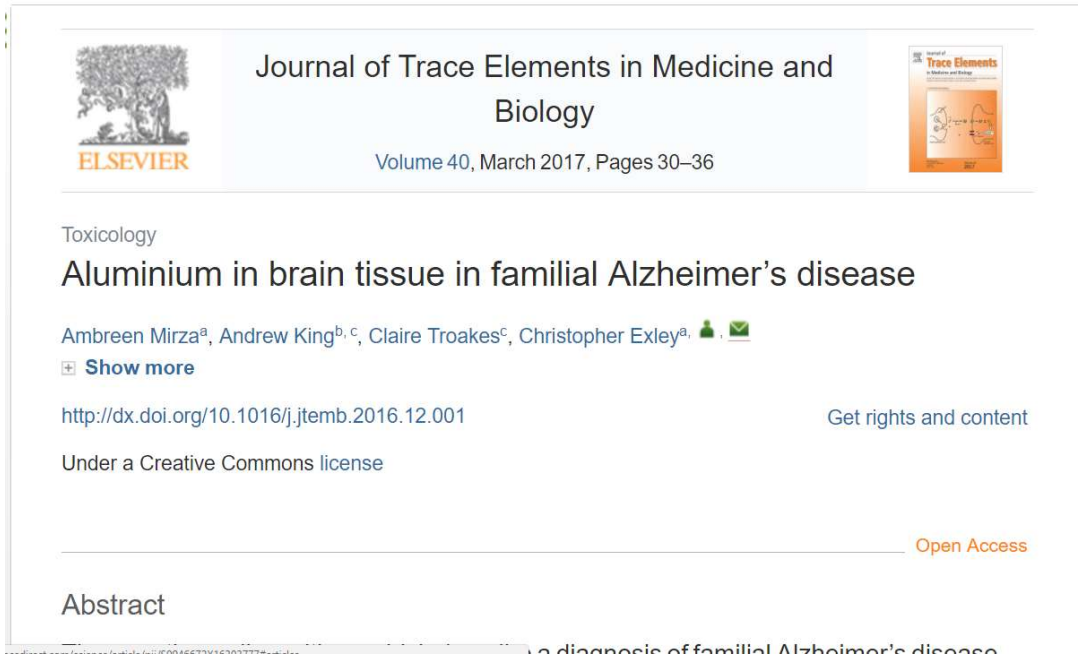
"…first ever measurements of aluminium in brain tissue from 12 donors diagnosed with familial Alzheimer's disease. The concentrations of aluminium were extremely high, for example, there were values in excess of **10 µg/g** tissue dry wt. in **5** of the 12 individuals. Overall, the concentrations were higher than all previous measurements of brain aluminium except cases of known aluminium-induced **encephalopathy**."

"we have previously recorded values up to *ca* **13.00 µg/g** in AD with occupational exposure to aluminium [14] and one value of **23.00 µg/g** in congophilic amyloid angiopathy (CAA) with environmental exposure to aluminium [13] the values measured herein for familial AD are more similar to those which have been associated with aluminium-induced encephalopathies"



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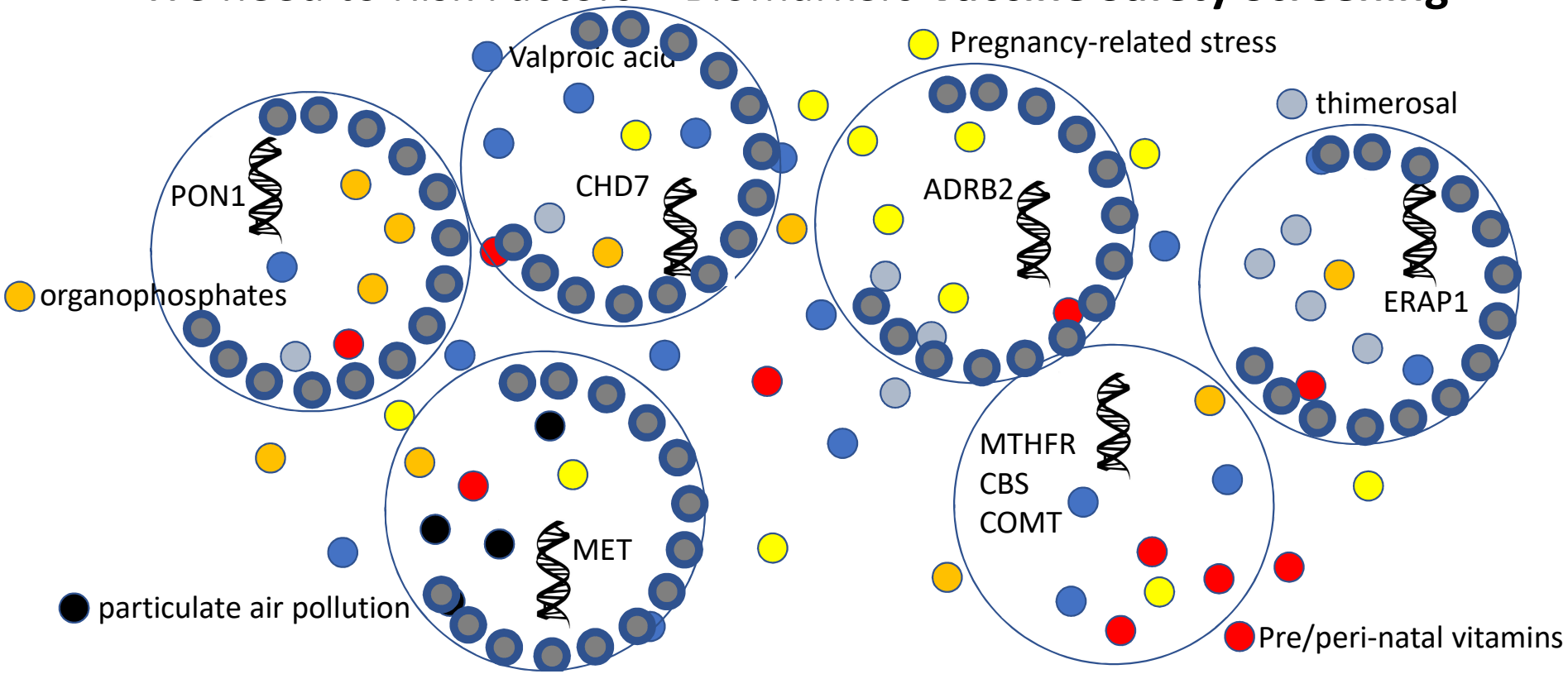
http://dx.doi.org/10.1016/j.jtemb.2016.12.001

Abstract

…a diagnosis of familial Alzheimer's disease

Environmental Toxin Liability Sampling Theory

- Aluminum levels in vaccines are unsafe
- We need to Risk Factors + Biomarkers **Vaccine Safety Screening**



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SCIENTIFIC REPORTS

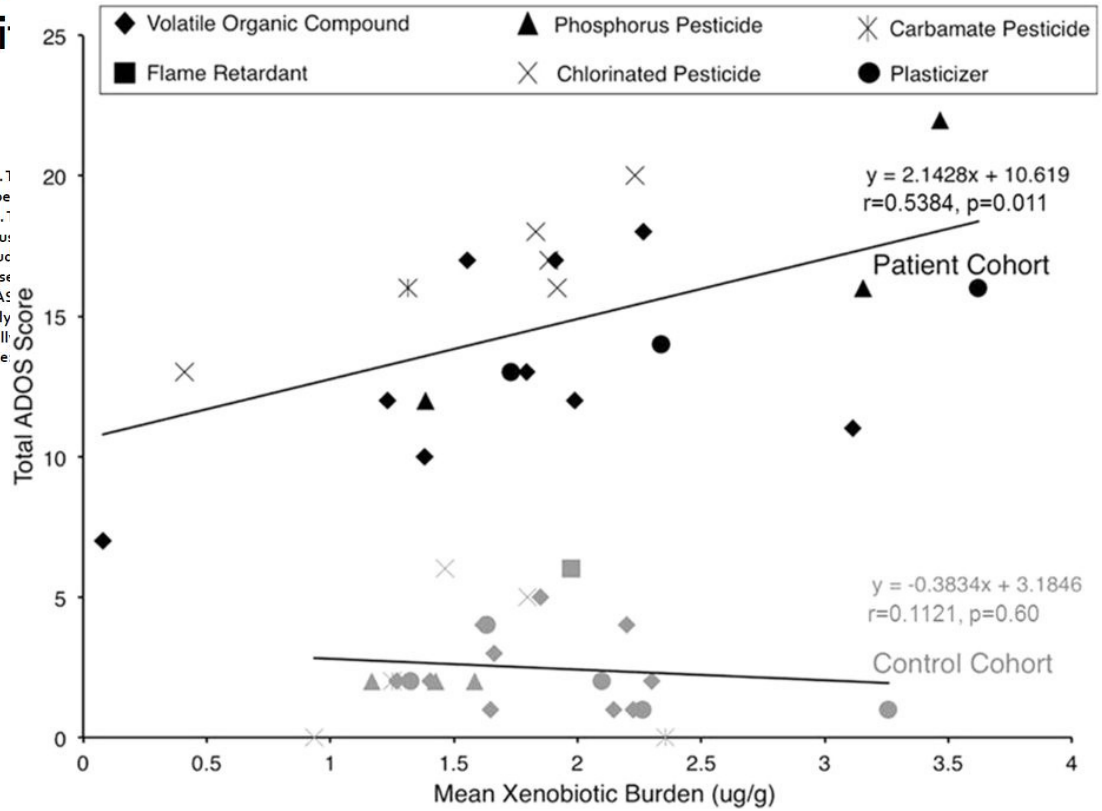
OPEN

Mean serum-level of common organic pollutants is predictive of behavioral severity in children wi autism spectrum disorders

Received: 08 December 2015
Accepted: 27 April 2016
Published: 13 May 2016

Andrew Boggess[1], Scott Faber[2], John Kern[3] & H. M. Skip Kingston[1]

Autism spectrum disorders (ASD), and their pathogenesis, are growing public health concerns. T study evaluated common organic pollutant serum-concentrations in children, as it related to be severity determined by rating scales and the Autism Diagnostic Observation Schedule (ADOS). T children, ages 2–9, with ASD and thirty controls matched by age, sex, and socioeconomic statu were evaluated using direct blood serum sampling and ADOS. Pooling concentrations of all stud pollutants into a single variable yielded cohort-specific neurobehavioral relationships. Pooled se concentration correlated significantly with increasing behavioral severity on the ADOS in the AS cohort ($p = 0.011$, $r = 0.54$), but not controls ($p = 0.60$, $r = 0.11$). Logistic regression significantly correlated mean pollutant serum-concentration with the probability of diagnosis of behaviorall severe autism, defined as ADOS >14, across all participants (odds ratio = 3.43 [95% confidence



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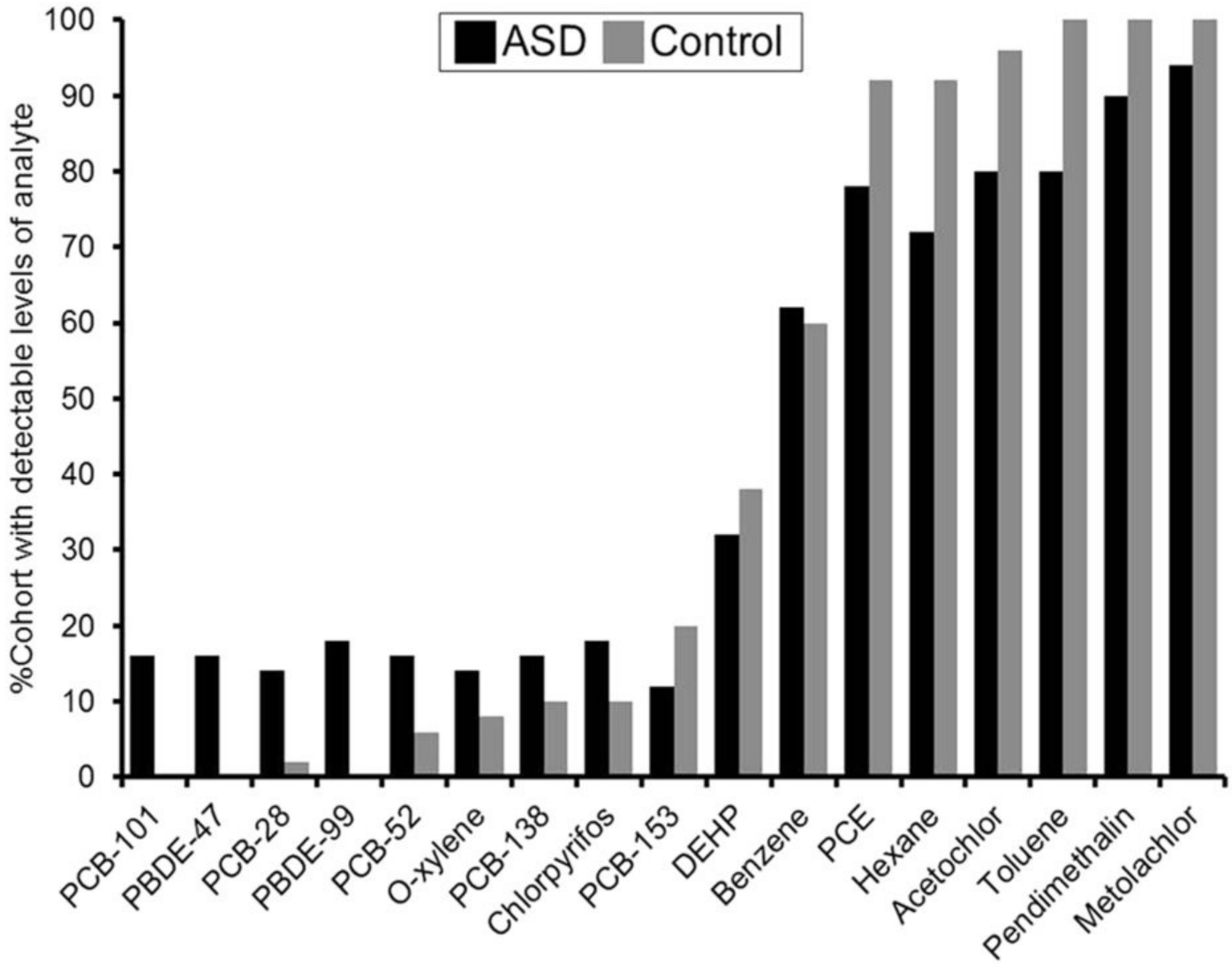


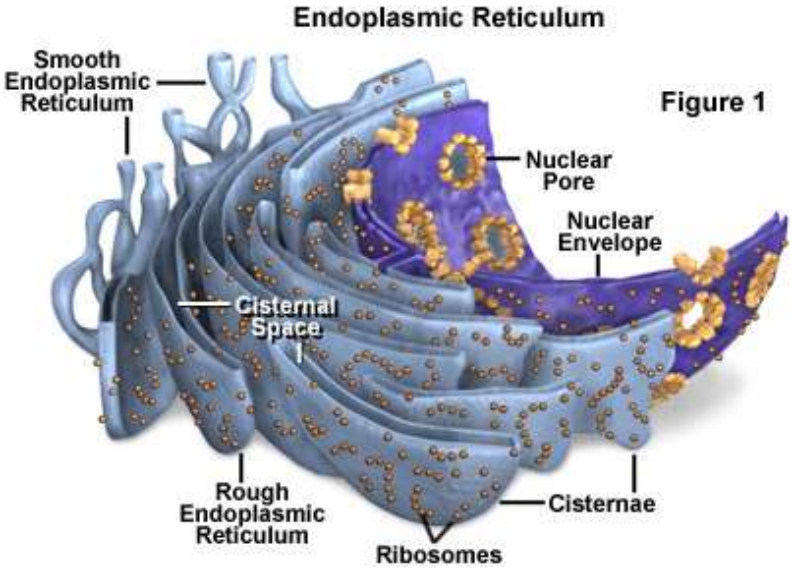
Molecular mimicry

- Mothers of autistics have anti-fetal brain antibodies
- Autistics tend to have anti-brain antibodies

Many mothers report being vaccinated during pregnancy.

Specific Mechanisms

- Mitopathies
- Chronic Microglial Activation (Excitotoxicity)
- Channelopathies
- Molecular mimicry
- Encephalopathy



https://micro.magnet.fsu.edu/cells/endoplasmicreticulum/endoplasmicreticulum.html

Manuel F. Casanova, M.D.

Gottfried and Gisela Kolb Endowed Chair in Psychiatry

Vice Chair for Research

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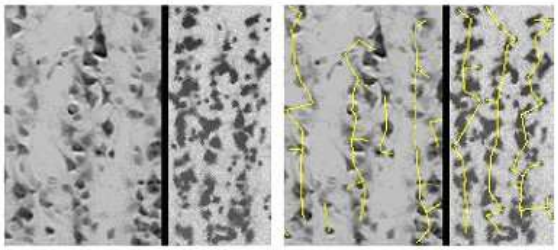
500 S Preston St Bldg 55A Ste 217
Louisville, Kentucky 40292-1702
Tel: 502-852-4077
Fax: 502-813-6665

E-mail: m0casa02@louisville.edu

Biosketch

Dr. Manuel Casanova made his residency training in n Johns Hopkins Hospital. During his stay at the Johns Hopkins Hospit ed his interest in developmental disorders of the brain. His clinical experience was enhanced by appoir land), the North Charles Hospital and the D.C. General Hospital. He spent several years as Deputy M the post-mortem examination of Sudden Infant Death Syndrome and child abuse. His expertise in the Armed Forces Institute of Pathology (AFIP) and as a Professorial Lecturer for the Department of Forensi to establish 2 of the most successful brain banks in this country: The Johns Hopkins Brain Resource Ce at the National Institutes of Mental Health (5 years). Dr. Casanova did training in psychiatry at the Danny Weinberger, and Joel Kleinman. He retired as a Major in the US Army Reserves and later on as a Georgia as a full Professor in 1991 and came to the University of Louisville in 2003 as the Gottfried ar

See also this Wikipedia entry.



A B

Figure 1. (A) The cortical section on the left is taken from a normal control patient, while the one on the right comes from an autistic patient. (B) The same image is shown overlaid with lines showing the columnar structure identified by our program. Both images contain three columns, but those in the control brain take up significantly more space than those in the other (67.8 μm v. 44.3 μm).

Research interests

Dr. Casanova has had over twenty years of experienc and neuropathology his interest has gradually shifted towards the study of abnormalities of cortical rate of 80 to 100 neurons having a common latency of response to stimulation. Using computerize olumn. His earlier work has reported interhemispheric differences in the morphometry of n lmann area 22—part of Wernicke's language region—the morphometric difference may play a role both in the development of language and in its disorders. His most recent studies have looked for the presence of abnormalities of minicolumnar organization and lateralization in the brains of patients who exhibit language disturbances, including autism, Asperger's syndrome, and dyslexia. He has summarized his work on minicolumns and provided an overview of the field in recent reviews of the literature appearing in Brain and Brain, Behavior and Evolution.

Online resources

- Dyslexia and talent, presented at the Dyslexic Advantage Conference on Dyslexia and Talent, 2013 July 19.
- Neurology Journals from The Lancet
- Cortical column article by Vernon B. Mountcastle at *Scholarpedia*
- Alopecia FAQ and coloring book
- Autism Netverse: A Literary Journey for the Autistic Mind
  Created by Vandna Jerath, co-author of the article "Autistic poetry as therapy"

Navigation

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- Citations, interviews, etc.
- Recent work
  - In press
  - Published
- Research interests
- Full CV

Elsewhere:

Cortical chauvinism weblog
Personal miscellany
IMFAR 2012 gallery
Alopecia info
Minicolumn.org top

doi:10.1093/brain/awt166 Brain 2013: 136; 2825–2835 | 2825

BRAIN
A JOURNAL OF NEUROLOGY

Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder

Mark D. Shen,[1] Christine W. Nordahl,[1] Gregory S. Young,[1] Sandra L. Wootton-Gorges,[2] Aaron Lee,[1] Sarah E. Liston,[1] Kayla R. Harrington,[1] Sally Ozonoff[1] and David G. Amaral[1]

1 The Medical Investigation of Neurodevelopmental Disorders (MIND) Institute and Department of Psychiatry and Behavioural Sciences, UC Davis School of Medicine, University of California, Davis, Sacramento, CA, USA
2 Department of Radiology, UC Davis School of Medicine and UC Davis Children's Hospital, University of California, Davis, Sacramento, CA, USA

Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders

Christine Wu Nordahl[a], Nicholas Lange[b], Deana D. Li[a], Lou Ann Barnett[a], Aaron Lee[a], Michael H. Buonocore[c], Tony J. Simon[a], Sally Rogers[a], Sally Ozonoff[a], and David G. Amaral[a,1]

[a]Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute and Department of Psychiatry and Behavioral Sciences, UC Davis School of Medicine, University of California, Sacramento, CA 95817; [b]Departments of Psychiatry and Biostatistics, Harvard University Schools of Medicine and Public Health, McLean Hospital, Belmont, MA 02478; and [c]Department of Radiology, UC Davis School of Medicine, University of California, Sacramento, CA 95817

Edited by James L. McGaugh, University of California, Irvine, CA, and approved October 19, 2011 (received for review May 12, 2011)

Autism is a heterogeneous disorder with multiple behavioral and biological phenotypes. Accelerated brain growth during early childhood is a well-established biological feature of autism. Onset pattern, i.e., early onset or regressive, is an intensely studied behavioral phenotype of

with autism report a 5–10% abnormal enlargement in total brain volume that persists into early childhood (11–13).

An altered trajectory of brain growth is now widely cited as central to the neuropathology of autism (3). However, several

Research in Autism Spectrum Disorders
Volumes 13–14, May 2015, Pages 15–24

Predicting the rate of language development from early motor skills in at-risk infants who develop autism spectrum disorder

Hayley C. Leonard[a, 2], Rachael Bedford[b, 2], Andrew Pickles[b], Elisabeth L. Hill[a], the BASIS Team[1],

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http://dx.doi.org/10.1016/j.rasd.2014.12.012

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Highlights

- Motor and social skills are closely related in typical and atypical development.
- The link between motor and language skills was examined in infants at-risk of ASD.
- Motor skills predicted rate of language development in infants who developed ASD.
- This relationship was evident for expressive but not receptive language.
- Research in ASD should focus on interactions between these systems over

LETTER

doi:10.1038/nature

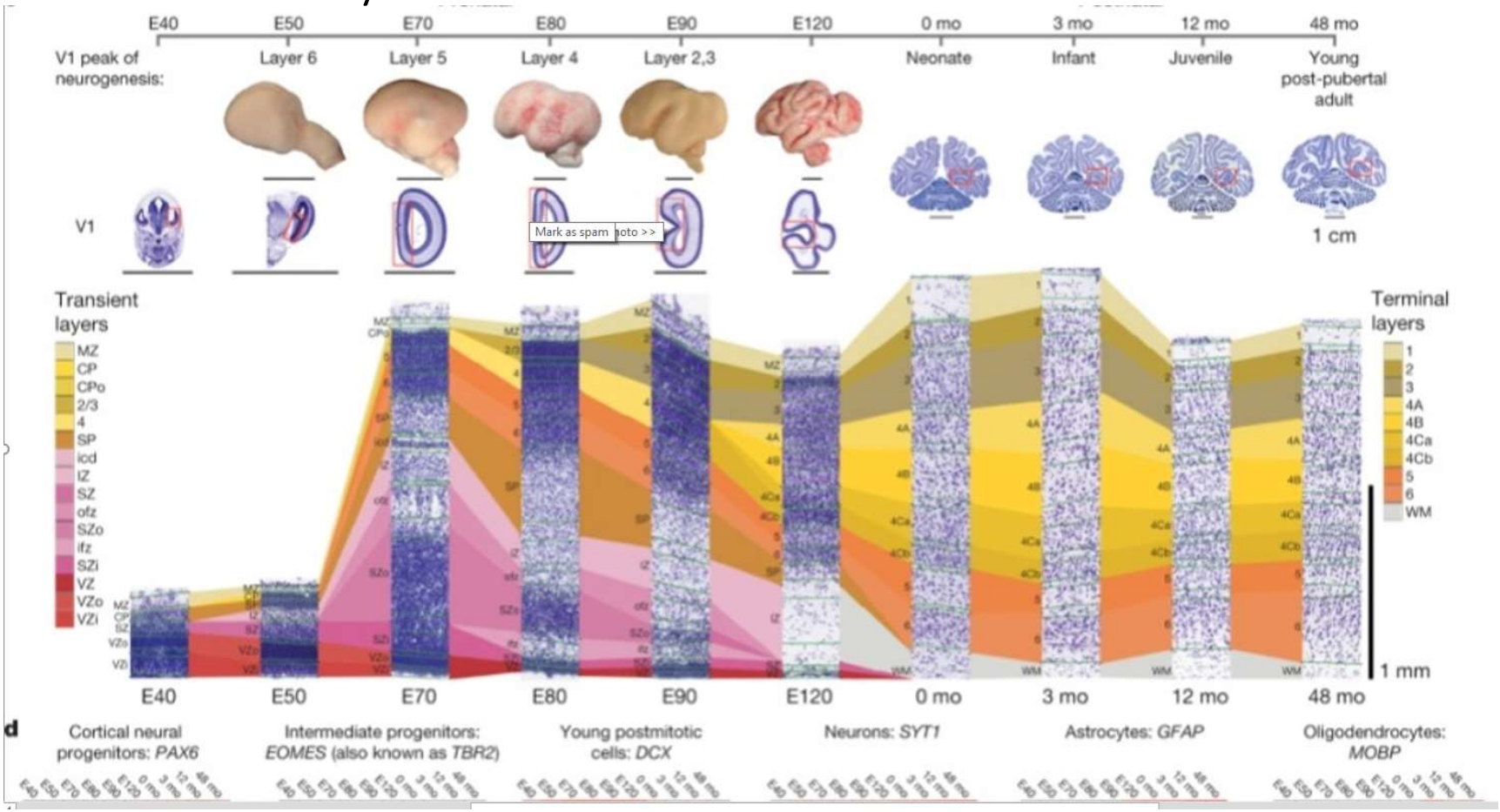
Early brain development in infants at high risk for autism spectrum disorder

Heather Cody Hazlett[1,2], Hongbin Gu[1], Brent C. Munsell[3], Sun Hyung Kim[1], Martin Styner[1], Jason J. Wolff[4], Jed T. Elison[5], Meghan R. Swanson[2], Hongtu Zhu[6], Kelly N. Botteron[7], D. Louis Collins[11], John N. Constantino[7], Stephen R. Dager[8,9], Annette M. Estes[9,10], Alan C. Evans[11], Vladimir S. Fonov[11], Guido Gerig[12], Penelope Kostopoulos[11], Robert C. McKinstry[13], Juhi Pandey[14], Sarah Paterson[15], John R. Pruett Jr[7], Robert T. Schultz[14], Dennis W. Shaw[8,9], Lonnie Zwaigenbaum[16], Joseph Piven[1,2] & the IBIS Network*

Brain enlargement has been observed in children with autism spectrum disorder (ASD), but the timing of this phenomenon, and the relationship between ASD and the appearance of behavioural symptoms, are unknown. Retrospective head circumference and longitudinal brain volume studies of two-year olds followed up

(see Methods for diagnostic and exclusion criteria). The three g
were comparable in (mean) race/ethnicity (85% white), family ir
maternal age at birth (33 years old), infant birth weight (8 lb), and
tional age at birth (39 weeks). The HR-ASD group had more male
the other two groups (83% of the HR-ASD group was male compared to

Neocortical Laminar Layers
Early Transient -> Mature Terminal



High-resolution transcriptional profiling of rhesus monkey brain development
(Bakken et al., Nature 2016)

2007

Block&Hong, 2007

LPS

BIOCHEMICAL SOCIETY TRANSACTIONS

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INFLAMMATION

Chronic microglial activation and progressive dopaminergic neurotoxicity

M.L. Block, J.-S. Hong

Biochemical Society Transactions
Nov 01, 2007;
35
(5)
1127-1132;
DOI: 10.1042/BST0351127

Article Figures Info & Metrics PDF

Abstract

PD (Parkinson's disease) is characterized by the selective and progressive loss of DA neurons (dopaminergic neurons) in the substantia nigra. Inflammation and activation of microglia, the resident innate immune cell in the brain, have been strongly linked to neurodegenerative diseases, such as PD. Microglia can respond to immunological stimuli and neuronal death to produce a host of toxic factors, including cytokines and ROS (reactive oxygen species). Microglia can also become persistently activated after a single stimulus and maintain the elevated production of both cytokines and ROS, long after the instigating stimulus is gone. Current reports suggest that this chronic microglial activation may be fuelled by either dying/damaged neurons or autocrine and paracrine signals from local glial cells, such as cytokines. Here, we review proposed mechanisms responsible for chronic neuroinflammation and explain the interconnected relationship between deleterious microglial activation, DA neuron damage and neurodegenerative disease.

Introduction

Microglia, the resident innate immune cells in the brain, are activated in response to neuronal

Honorary Editor
Colin Bingle
Department of Infection and Immunity, University of Sheffield

November 2007

Volume: 35 Issue: 5

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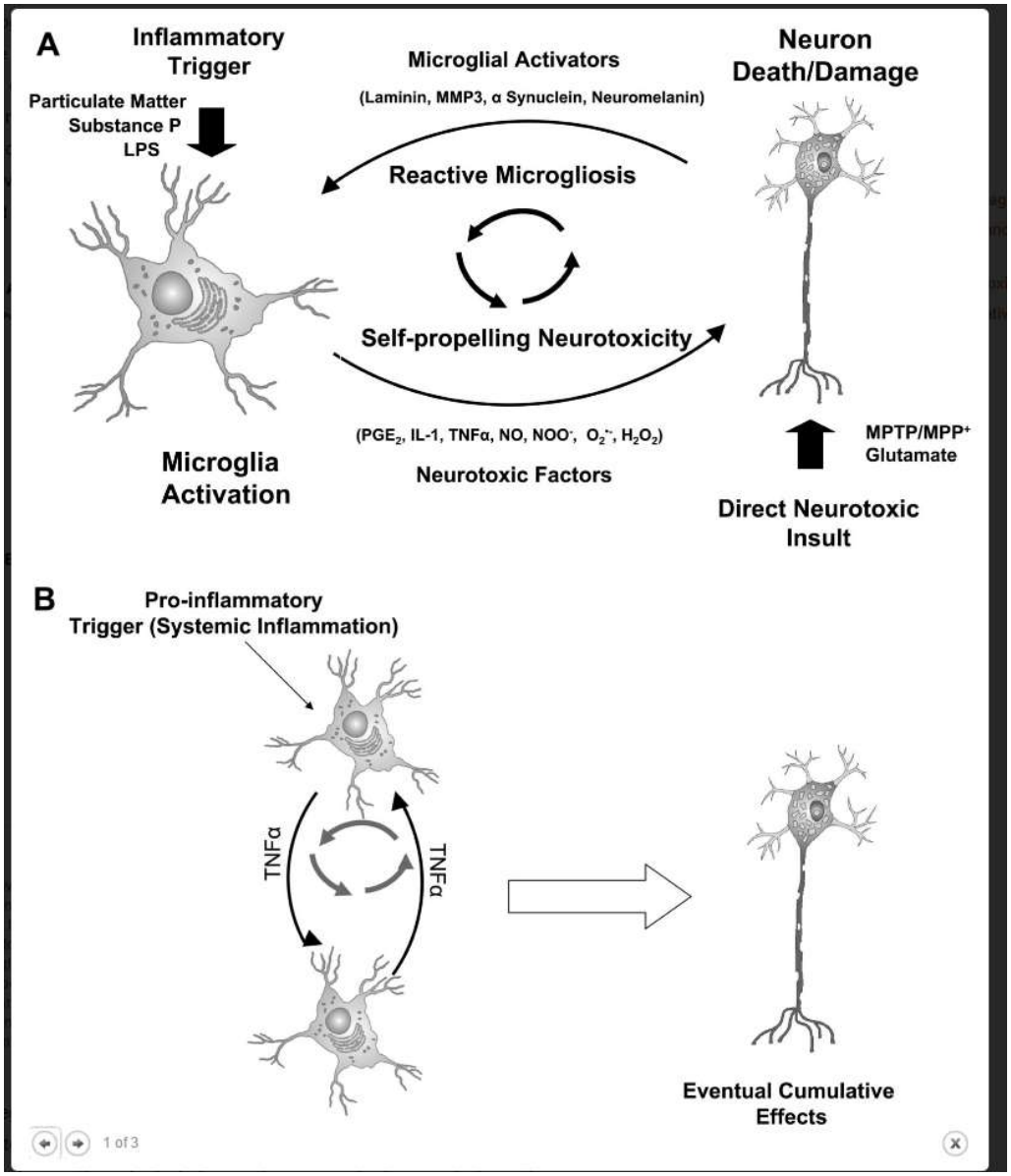
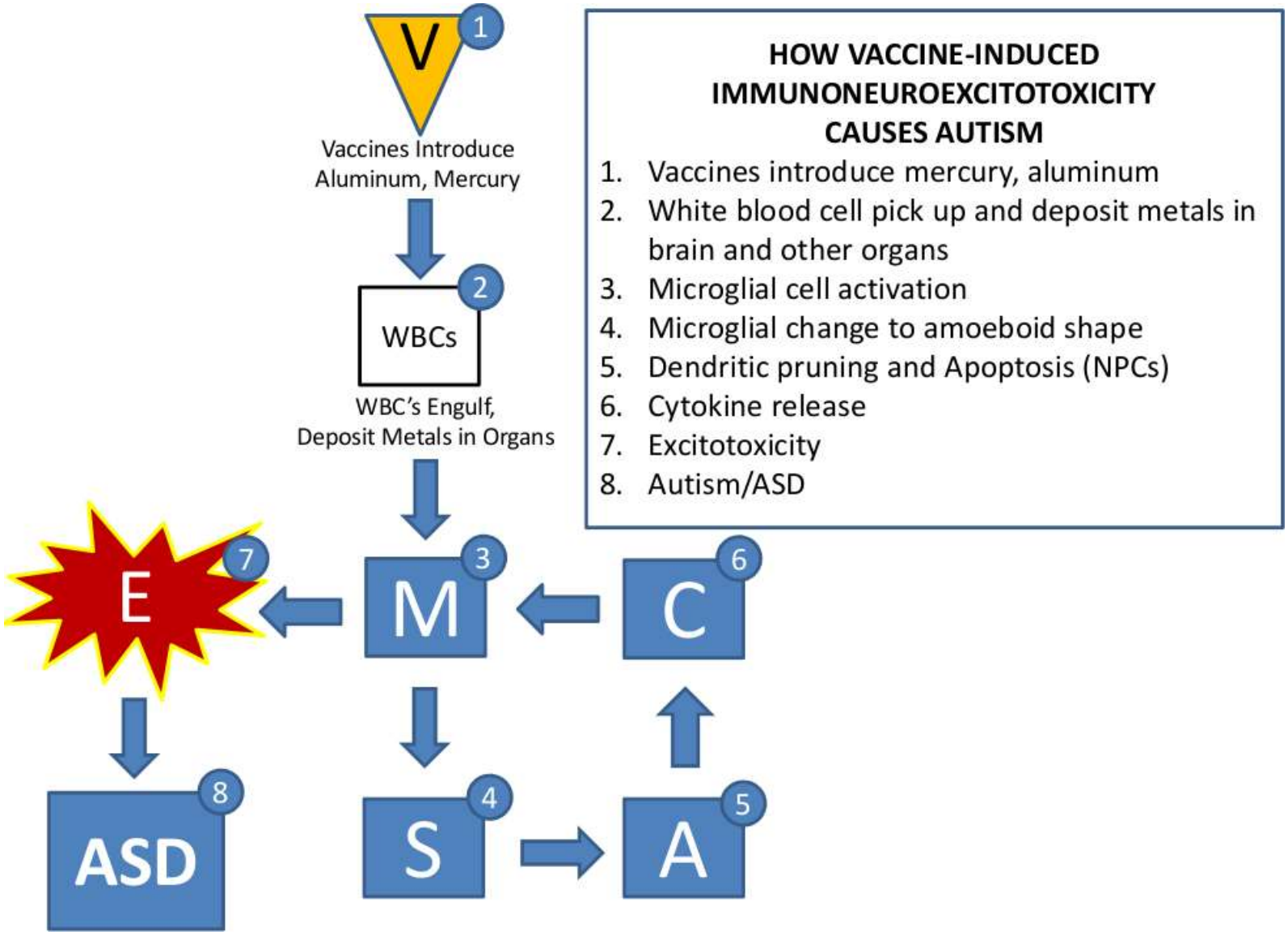
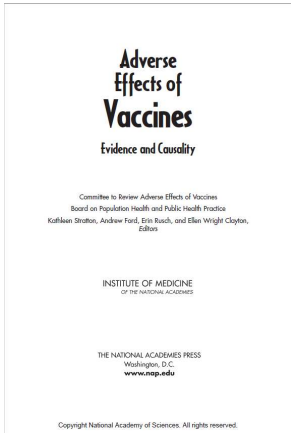
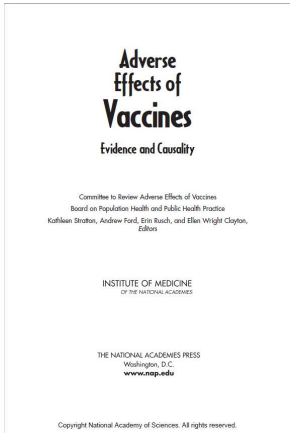




HOW VACCINE-INDUCED IMMUNONEUROEXCITOTOXICITY CAUSES AUTISM

1. Vaccines introduce mercury, aluminum
2. White blood cell pick up and deposit metals in brain and other organs
3. Microglial cell activation
4. Microglial change to amoeboid shape
5. Dendritic pruning and Apoptosis (NPCs)
6. Cytokine release
7. Excitotoxicity
8. Autism/ASD





IOM 2004
"insufficient evidence exists"

IOM 2012:
Rejected 17/22 studies as flawed:

*"The **five** remaining controlled studies (Farrington et al., 2001; Madsen et al., 2002; Mrozek-Budzyn et al., 2010; Smeeth et al., 2004; Taylor et al., 1999) contributed to the weight of epidemiologic evidence and are described below."*

“NO STUDY HAS EVER SHOWN”

- [x] ANALYZE THE DATA REPEATEDLY UNTIL THE POSITIVE ASSOCIATION “GOES AWAY”
- [x] CHANGE THE RESULTS POST-PEER REVIEW, POST-PUBLICATION, IN PLAIN SITE (UNO ET AL.)
- [x] USE THE MOST CONSERVATIVE METHOD FOR MULTIPLE HYPOTHESIS TESTING (BONFERRONI)
- [x] CHANGE THE RESULTS POST-PEER REVIEW, POST-PUBLICATION, IN PLAIN SITE (UNO ET AL.)
- [x] USE THE MOST CONSERVATIVE METHOD FOR MULTIPLE HYPOTHESIS TESTING (BONFERRONI)
- [x] OVERFIT THE MODEL USING REDUNDANT, HIGHLY COLLINEAR VARIABLES
- [x] REMOVE PATIENTS WHO ARE LIKELY TO HAVE ASD FEATURES
- [x] “CORRECT FOR” COVARIATES RELATED TO ASD
- [x] REDUCE SAMPLE SIZE TO REDUCE POWER TO DETECT ASSOCIATION
- [x] CHANGE STUDY DESIGN POST FACTO TO SEE IF ASSOCIATION CAN BE LOST
- [x] FAIL TO REPORT INITIAL ASSOCIATION
- [x] CHANGE CONTINUOUS VARIABLES TO DISCRETE (CUM. EXPOSURE -> “ON TIME” VS. “LATE”

Why Association Studies Mean Nothing

- "No association" → "Low power to detect"
- "No association" → "After we analyzed it 10 ways to make the association go away"
- "No association" → "After we removed all results showing no association"

- "No association" → "No Universal Effect"

Autism rates are between 0-3%.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B[1] (HepB)	2 STUDIES SHOW ASSOCIATION															
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			0 STUDIES EXIST													
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			6 STUDIES SHOW ASSOCIATION													
Haemophilus influenzae type b[4] (Hib)			2 STUDIES SHOW ASSOCIATION													
Pneumococcal conjugate[5] (PCV13)			0 STUDIES EXIST													
Inactivated poliovirus[6] (IPV: <18 yrs)			0 STUDIES EXIST													
Influenza[7] (IIV; LAIV)					0 STUDIES EXIST											
Measles, mumps, rubella[8] (MMR)					2 POSITIVE AND MANY NEGATIVE "STUDIES" EXIST RE: Thompson											
Varicella[9] (VAR)							1 STUDY SHOWS ASSOCIATION									
Hepatitis A[10] (HepA)							1 STUDY SHOWS ASSOCIATION									
Meningococcal[11] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)			0 STUDIES – GBS, PARALYSIS (NUMEROUS)													
Tetanus, diphtheria, & acellular pertussis[12] (Tdap: ≥7 yrs)													N/A			
Human papillomavirus[13] (2vHPV: females only; 4vHPV, 9vHPV: males and females)														N/A		
Meningococcal B[11]														N/A		
Pneumococcal polysaccharide[5] (PPSV23)											0 STUDIES					

"VACCINES DO NOT CAUSE AUTISM" - CDC

Environmental Exposures During Pregnancy

- Folic acid (prenatal vitamins)
- Mercury (Seafood [tuna/swordfish], Hg dental amalgams)
- Mold toxicity
- Roadside aluminum dust
- Glyphosate (RoundUp™)
- Vaccines
  - TDaP/DTaP – for whooping cough
  - Influenza vaccine w/thimerosal
  - Accidental MMR and others contraindicated during pregnancy

Potential Risk Factors/Biomarkers

- Antibrain protein antibodies — Rossi et al., 2013; see Braunschweig et al., 2012
- Low immunoglobulin levels — Grether et al. (2016)
- Parental age, income, %tile body weight, Vit D3, familial history, etc.

CHD7, CHD8, KATNAL2, SCN1A, SCN2A, MeCP2, AUTS2, NRXN1, MTHFS, CACNA1G, GRM5, GABA-β3 receptor subunit, MTCO1, MTCO2, SLC25A12, PIK3CA, GIRDIN, CNTN5, CNTN6, IMMP2L, MCPH1, HOXA, microcephalin 1, GRIN2, GRIN2B, GRIN2A, GRIN2C, GRM7, CTNND2, CNTN4, NRXN1, PARK2, FOXP1, LAMC3, GluR6, GluR8, ARID1B, SETD2, BDNF, MAO-A, 5-HT2A serotonin receptor, PRKCB1, CD13, GRM3, HRAS, NRXN1, GNB2L1, MKNK2, OXTR

Vaccine Adverse Events in the NICU

Reports of increases in

- Sepsis evaluation
- Intubation
- SIDS
- Failure to Thrive
- “Sleep-related”

Research

Original Investigation

Adverse Events After Routine Immunization of Extremely Low-Birth-Weight Infants

Stephen D. DeMeo, DO; Sudha R. Raman, PhD; Christoph P. Hornik, MD, MPH; Catherine C. Wilson, DNP, NNP-BC, FNP-BC; Reese Clark, MD; P. Brian Smith, MD, MPH, MHS

Editorial page 718

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Clinical Associations with Immature Breathing in Preterm Infants:

Part 2: Periodic Breathing

Manisha Patel[1], **Mary Mohr**[3], **Douglas Lake**[2], **John Delos**[3], **J. Randall Moorman**[2], **Robert Sinkin**[1], **John Kattwinkel**[1], and **Karen Fairchild**[1]

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[3] Department of Physics, The College of William and Mary, Williamsburg, VA 23187

Abstract

Background—Periodic breathing (PB) is a normal immature breathing pattern in neonates that, if extreme, may be associated with pathologic conditions.

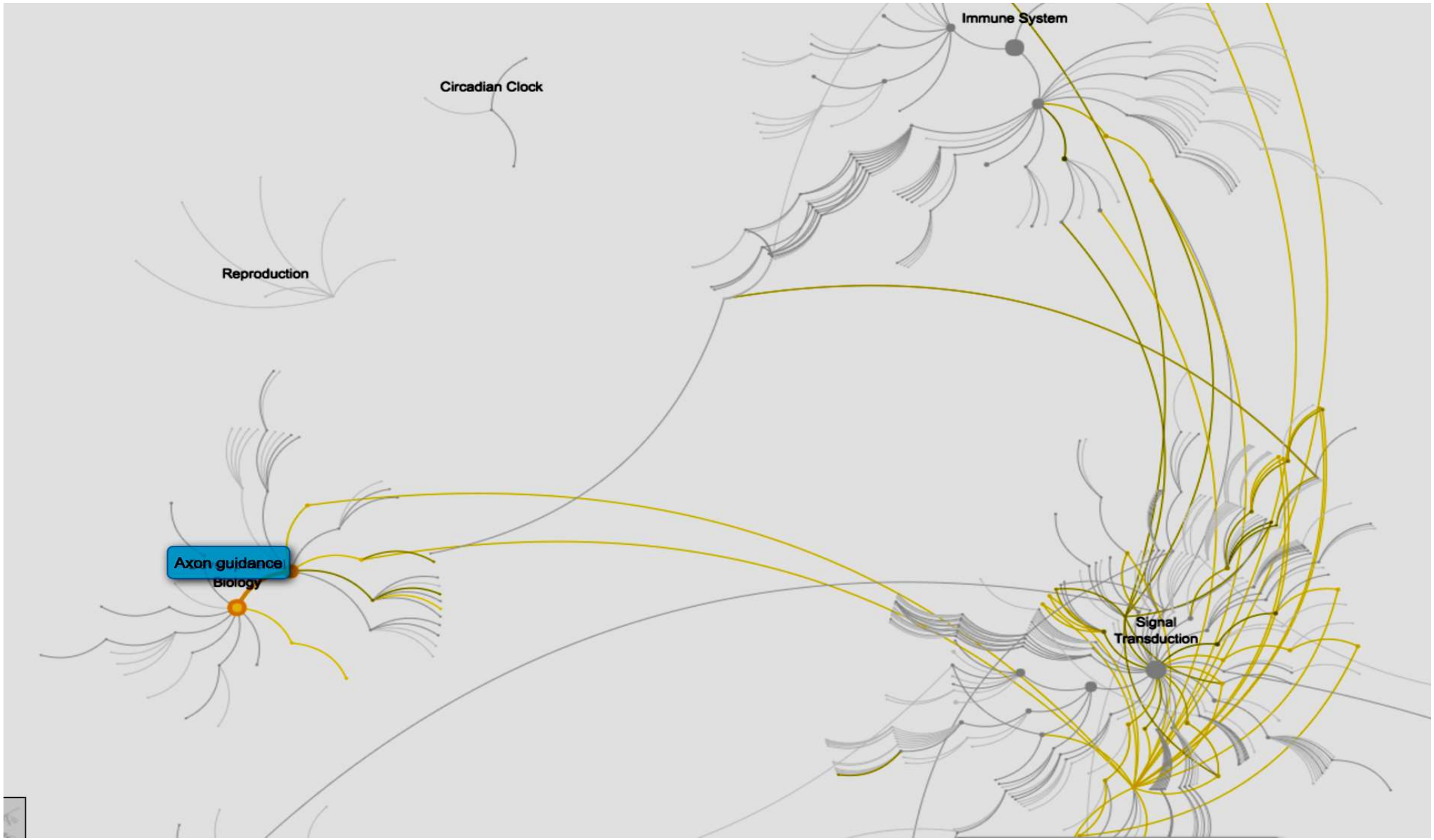
Methods—We used our automated PB detection system to analyze all bedside monitor chest

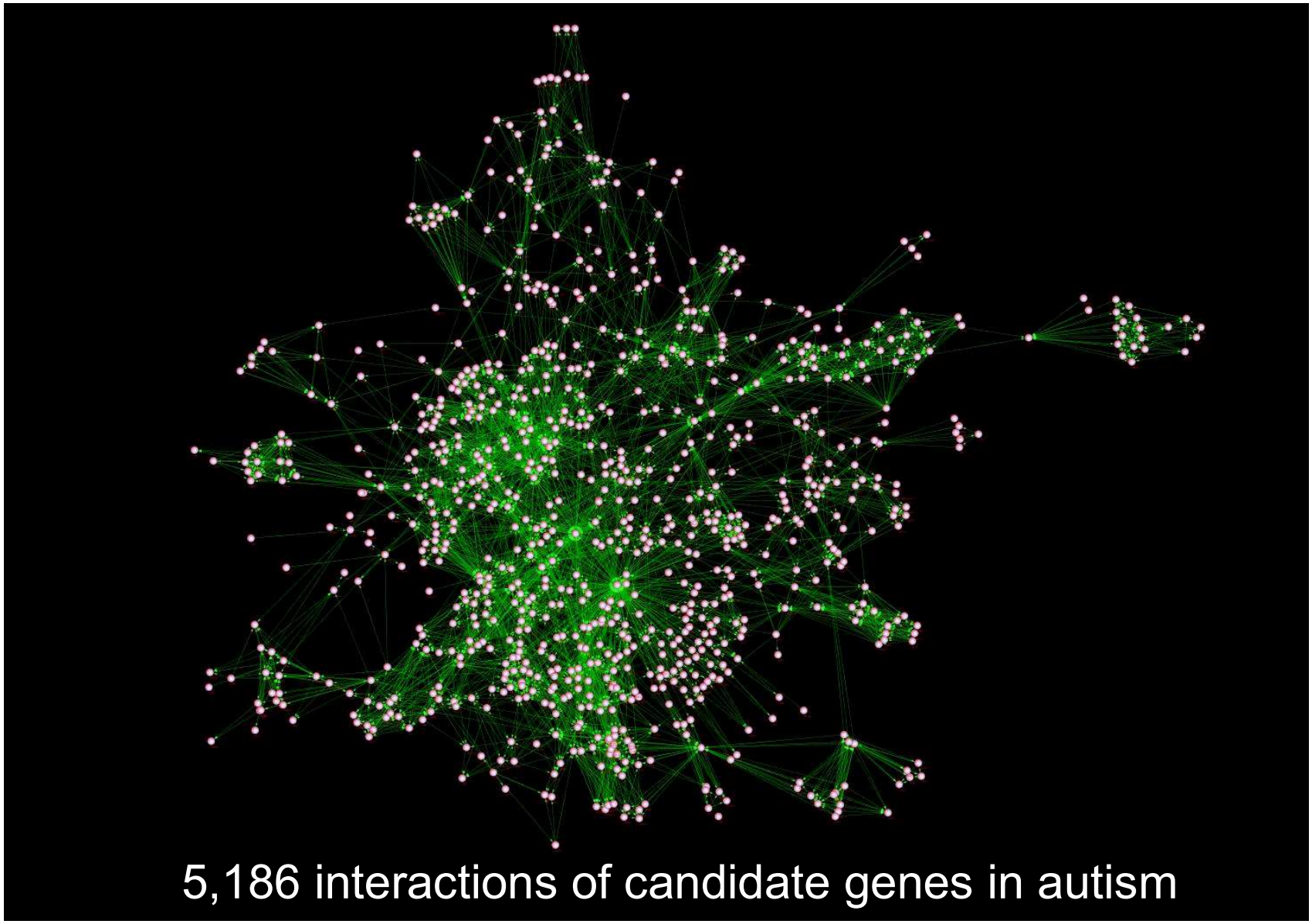
G x E Interactions
Bowers & Erickson (2014) Review

- Organophosphates <-> PON1 gene
- Pregnancy-related stress <-> ADRB2 gene
- Traffic-related particulate matter (pollution) <-> MET gene

- Periconceptional maternal prenatal vitamin <-> (MTHFR, CBS, COMT)

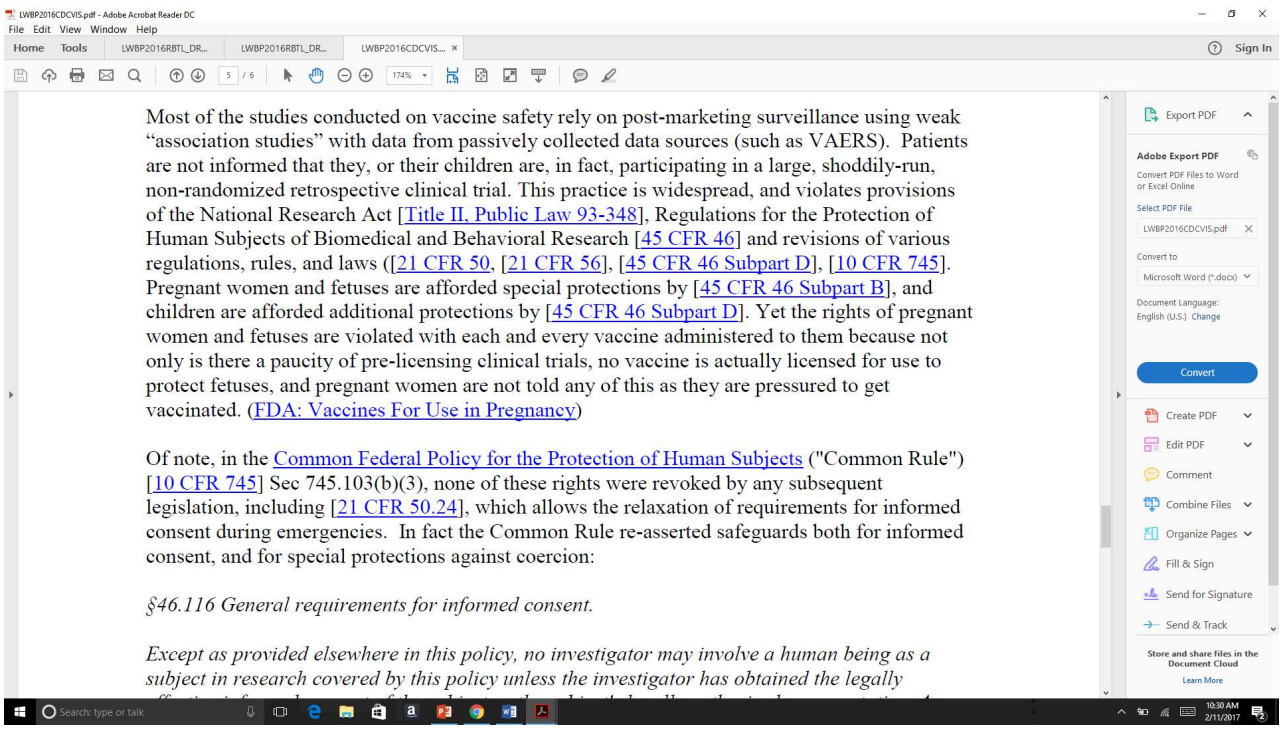
- Bowers K, C. Erickson. 2014. Gene-environment interaction and autism spectrum disorder. OA Autism 2(1):3.


Immune System
Circadian Clock
Reproduction
Axon guidance
Biology
Signal
Transduction


5,186 interactions of candidate genes in autism

Relevant Rulings, Regulations, and Law

- National Childhood Vaccine Injury Act (NVCIA) of 1986 42 USC 300aa-1 to 300aa-34
- Supreme Court Ruling "Unavoidably unsafe"
- 21st Century Cures Act
- Many regulations on Informed consent ------->



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Most of the studies conducted on vaccine safety rely on post-marketing surveillance using weak "association studies" with data from passively collected data sources (such as VAERS). Patients are not informed that they, or their children are, in fact, participating in a large, shoddily-run, non-randomized retrospective clinical trial. This practice is widespread, and violates provisions of the National Research Act [Title II, Public Law 93-348], Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research [45 CFR 46] and revisions of various regulations, rules, and laws ([21 CFR 50, [21 CFR 56], [45 CFR 46 Subpart D], [10 CFR 745]. Pregnant women and fetuses are afforded special protections by [45 CFR 46 Subpart B], and children are afforded additional protections by [45 CFR 46 Subpart D]. Yet the rights of pregnant women and fetuses are violated with each and every vaccine administered to them because not only is there a paucity of pre-licensing clinical trials, no vaccine is actually licensed for use to protect fetuses, and pregnant women are not told any of this as they are pressured to get vaccinated. (FDA: Vaccines For Use in Pregnancy)

Of note, in the Common Federal Policy for the Protection of Human Subjects ("Common Rule") [10 CFR 745] Sec 745.103(b)(3), none of these rights were revoked by any subsequent legislation, including [21 CFR 50.24], which allows the relaxation of requirements for informed consent during emergencies. In fact the Common Rule re-asserted safeguards both for informed consent, and for special protections against coercion:

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally

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Pace Environmental Law Review

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Issue 2 *Winter 2011*

Article 6

January 2011

Unanswered Questions from the Vaccine Injury Compensation Program: A Review of Compensated Cases of Vaccine-Induced Brain Injury

Mary Holland
NYU School of Law, hollandm@exchange.law.nyu.edu

Louis Conte

Robert Krakow

Lisa Colin

83 Instances of dx
of autism in awarded cases

Family Law Trends

- “Midnight” invocation of vaccination refusal prior to custody decisions
- >300 State bills to remove non-medical exemptions
- Last-ditch vaccine concerns in custody (divorce)
  - Courts tend to side w/parent who claims they will vaccinate
- Attorney/Client relationship violated (El Paso, TX)

- Quiet regulatory shifts being explored
  - Moves to mandate vaccination for entry into preschool
  - (Obama HHS “Corrective Action”-> Region V states, esp. MI and OH)

Parental Refusal of Childhood Vaccines and Medical Neglect Laws

Efthimios Parasidis, JD, MBioethics, and Douglas J. Opel, MD, MPH

Objectives. To examine the relation of vaccine refusal and medical neglect under child welfare laws.

Methods. We used the Westlaw legal database to search court opinions from 1905 to 2016 and identified cases in which vaccine refusal was the sole or a primary reason in a neglect proceeding. We also delineated if religious or philosophical exemptions from required school immunizations were available at the time of adjudication.

Results. Our search yielded 9 cases from 5 states. Most courts (7 of 9) considered vaccine refusal to constitute neglect. In the 4 cases decided in jurisdictions that permitted religious exemptions, courts either found that vaccine refusal did not constitute neglect or considered it neglect only in the absence of a sincere religious objection to vaccination.

Conclusions. Some states have a legal precedent for considering parental vaccine refusal as medical neglect, but this is based on a small number of cases. Each state should clarify whether, under its laws, vaccine refusal constitutes medical neglect. (*Am J Public Health.* 2017;107:68–71. doi:10.2105/AJPH.2016.303500)

Parental refusal of childhood vaccines is a contentious issue in pediatrics and

result in harm to the child) constitute child maltreatment.

reports solely based on failure to vaccinate,[6] and Michigan has an explicit policy to this effect.[7] A few states codify that vaccine refusal regardless of reason,[8] or solely for sincere religious beliefs,[9] does not constitute medical neglect. Furthermore, even if vaccine refusal amounts to medical neglect, it is not clear that this finding requires state intervention. Ross and Aspinwall[10] contend that there should be a distinction between medical neglect and state intervention, arguing that vaccine refusal constitutes the former but does not warrant the latter. Chervenak et al.[4] argue that the purpose of reporting parents who refuse childhood vaccines to CPS for neglect is not to provoke "highly intrusive measures," such as loss of custody, but to "engage [CPS] in further efforts to persuade the parents."(p308) Simply invoking CPS, however, may undermine parents' views of

www.cnn.com/2017/02/15/health/thimerosal-vaccine-preservative-explainer/

CNN Health » Diet + Fitness | Living Well | Parenting + Family — Live TV — U.S. Edition +

Thimerosal: Everything you need to know about this vaccine preservative

By Jen Christensen, CNN
Updated 7:52 AM ET, Wed February 15, 2017

Source: CNN

NIH doctor debunks celebrities on vaccines 04:36

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House panel investigates handling of info at Mar-a-Lago

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Loan type 15-Year Fixed

APR 3.20%

CDC A-Z INDEX

The science is clear: Vaccines are safe, effective, and do not cause autism

Johns Hopkins public health expert Daniel Salmon discusses vaccine safety and the potential hazards pose by fewer children being vaccinated

Childhood vaccines are safe. Seriously.

By Jen Christensen and Nadia Kounang, CNN
Updated 3:18 PM ET, Tue July 1, 2014

Source: CNN

Should I get my child vaccinated? 01:14

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Tapper to Trump: Media didn't fire Flynn, you did

Little Caesars founder quietly paid Rosa Parks' rent for years

Story highlights

Review of more than 20,000 scientific titles and 67 papers finds no evidence linking vaccines, autism

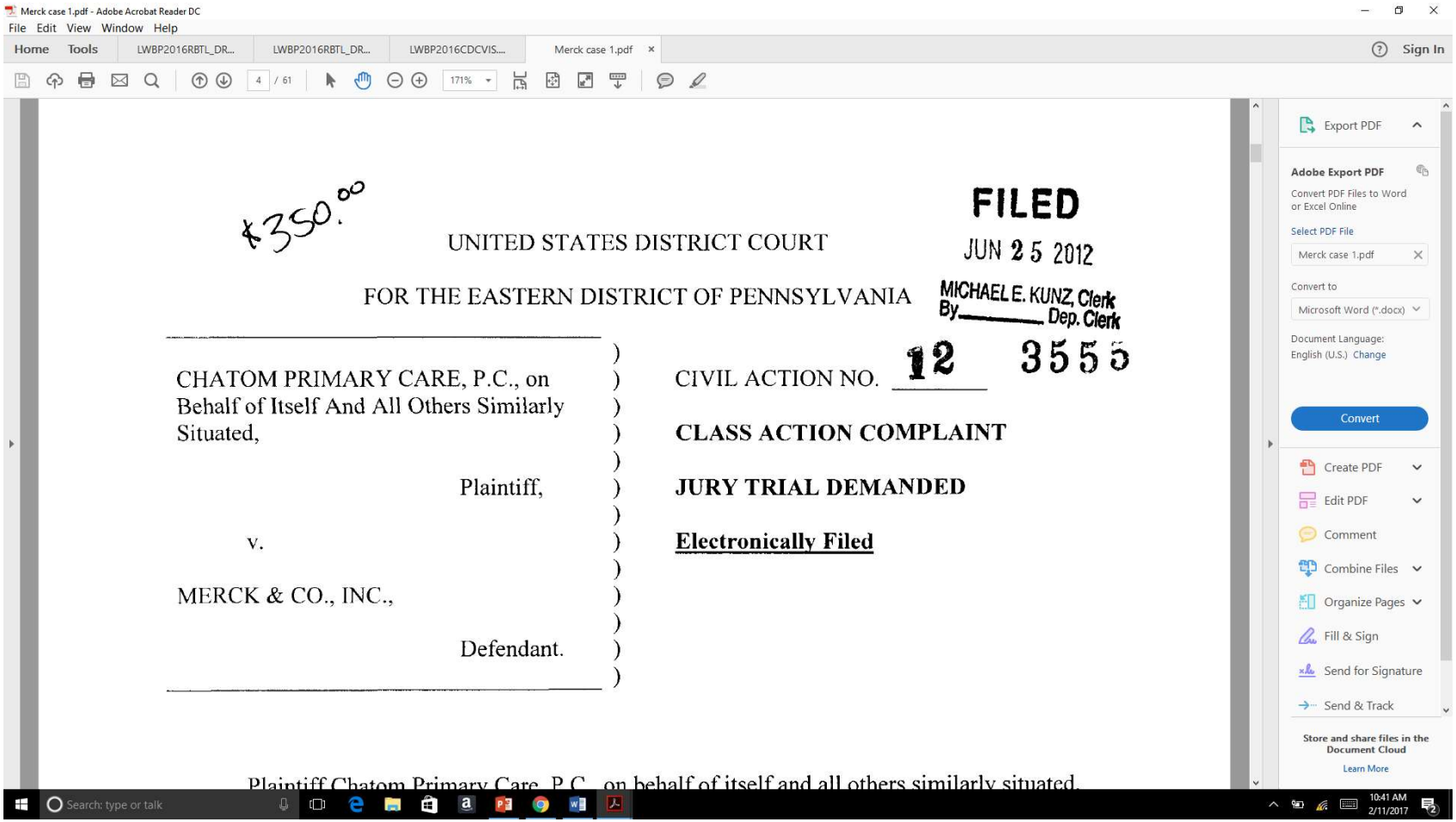
Children should get vaccinated against preventable and potentially deadly diseases. Period.

That's what a project that screened more than 20,000 scientific titles and 67 papers on vaccine safety

lendingtree

Today's Mortgage Rates
3.20%
APR 15-Year Fixed

Merck Fraud on Efficacy?



brings this action against Merck & Co., Inc. ("Merck" or "Defendant"), and alleges as follows, based on information and belief, counsel's investigation, and a *qui tam* action filed by Stephen A. Krahling and Joan A. Wlochowski (the "Relators") captioned *Krahling v. Merck & Co., Inc.*, 2:10-cv-04374-CDJ (E.D. Pa.) (the "*Qui Tam* Action"):

INTRODUCTION

1. Merck is the exclusive supplier of mumps vaccine (including M-M-R®II and ProQuad®) (collectively, "Mumps Vaccine") in the U.S.

2. This lawsuit is brought as a proposed class action against Merck for unlawfully monopolizing the U.S. market for Mumps Vaccine by engaging in a decade-long scheme to falsify and misrepresent the true efficacy of its vaccine.

3. Specifically, Merck fraudulently represented and continues to falsely represent in its labeling and elsewhere that its Mumps Vaccine has an efficacy rate of 95 percent or higher.

In reality, Merck knows and has taken affirmative steps to conceal -- by using improper testing techniques and falsifying test data -- that its Mumps Vaccine is, and has been since at least 1999, far less than 95 percent effective.

4. Merck manufactures its Mumps Vaccine using an attenuated virus. An attenuated virus is created when its pathogenicity has been reduced so that it will initiate an immune response without producing the specific disease. Pathogenicity is reduced by "passaging" the virus through a series of cell cultures or animal embryos. With each passage, the virus becomes better at replicating in the host, but loses its ability to replicate in human cells. Eventually, the attenuated virus will be unable to replicate well (or at all) in human cells, and can be used in a vaccine. When this vaccine is administered to a human, the virus in it will be unable to replicate enough to cause illness, but will still provoke an immune response that can protect against future infection.

5. However, Merck knew and understood that the continued passaging of the

2 Whistleblower Allegations:

- Tried 2 flawed methodologies to show >95%
- Both failed. Falsified efficacy (ADDED *Rabbit* Antibodies)
- Submitted falsified efficacy results to FDA.
- Concealed fraud
- Continue to conceal fraud after mumps outbreaks in 2006, 2009
- Sold hundreds of millions of vials of ineffective vaccine

The Washington Post
Democracy Dies in Darkness

Health & Science

AP Explains: Why there's a US surge in mumps despite vaccine

FILE - In this Jan. 16, 1957 file photo, Jon Douglas, 6, right, visits his friend, Greg Cox, standing behind a sign warning he has mumps, on the

AP Explanation:

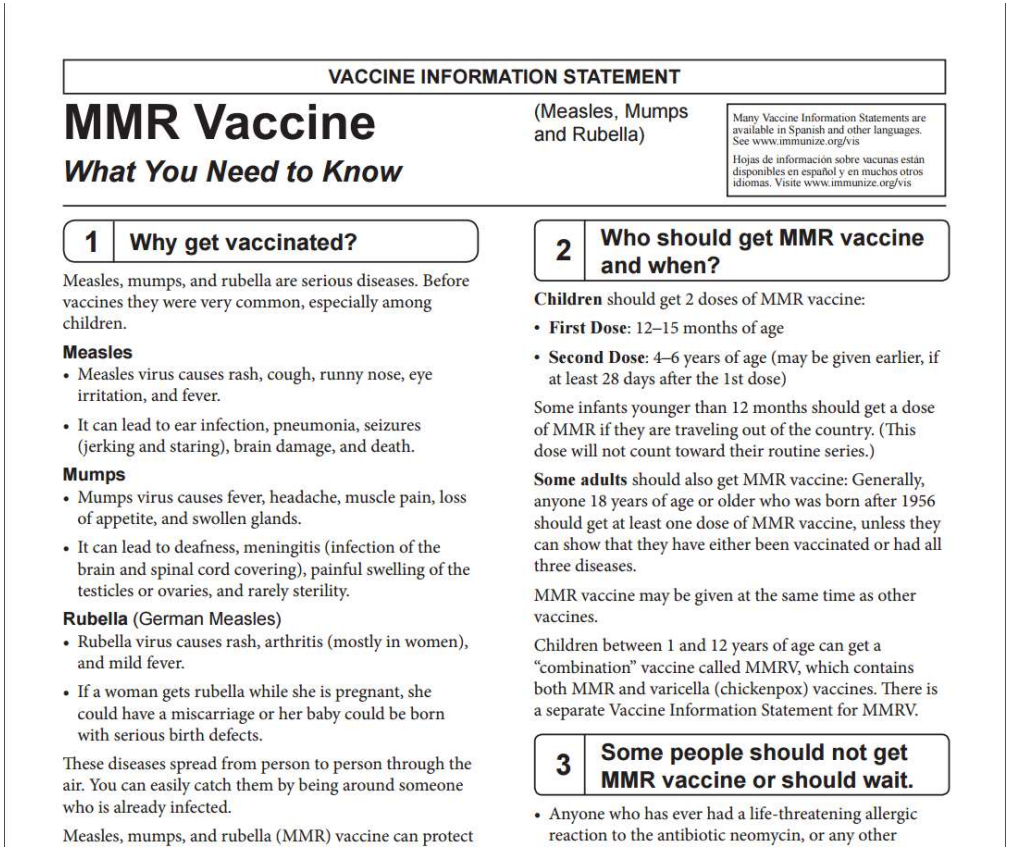
- “No vaccine is perfect and it's expected that some people who get the shots will still get mumps. Also, some research suggests that 10 or more years after the second dose, immunity may fade enough to allow outbreaks to take hold. During some outbreaks, like one currently at the University of Missouri, students and others have been offered a third booster dose to increase protection and snuff out the outbreak.”

The Constitution of United States of America 1789 (rev. 1992) First Amendment

- *"Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the Government for a redress of grievances."*
- *In late 2016, in response to a Notice from CDC Posted in the Federal Register, Vol. 81, No. 201 of Tuesday, October 18, 2016 for a call for* ***public comments*** *re: Proposed Revised Vaccine Information Materials for MMR (Measles, Mumps, and Rubella and MMRV (Measles, Mumps, Rubella, and Varicella Vaccines)…*

Public Comments: MMR and MMR-V VIS Experience (2016/2017)

- Proposed weakening the information on risk
- Call for Public Comments
- Anyone can access the comments



VACCINE INFORMATION STATEMENT

MMR Vaccine (Measles, Mumps and Rubella)

What You Need to Know

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis

Hojas de información sobre vacunas están disponibles en español y en muchos otros idiomas. Visite www.immunize.org/vis

1 Why get vaccinated?

Measles, mumps, and rubella are serious diseases. Before vaccines they were very common, especially among children.

Measles

- Measles virus causes rash, cough, runny nose, eye irritation, and fever.
- It can lead to ear infection, pneumonia, seizures (jerking and staring), brain damage, and death.

Mumps

- Mumps virus causes fever, headache, muscle pain, loss of appetite, and swollen glands.
- It can lead to deafness, meningitis (infection of the brain and spinal cord covering), painful swelling of the testicles or ovaries, and rarely sterility.

Rubella (German Measles)

- Rubella virus causes rash, arthritis (mostly in women), and mild fever.
- If a woman gets rubella while she is pregnant, she could have a miscarriage or her baby could be born with serious birth defects.

These diseases spread from person to person through the air. You can easily catch them by being around someone who is already infected.

Measles, mumps, and rubella (MMR) vaccine can protect

2 Who should get MMR vaccine and when?

Children should get 2 doses of MMR vaccine:

- **First Dose**: 12–15 months of age
- **Second Dose**: 4–6 years of age (may be given earlier, if at least 28 days after the 1st dose)

Some infants younger than 12 months should get a dose of MMR if they are traveling out of the country. (This dose will not count toward their routine series.)

Some adults should also get MMR vaccine: Generally, anyone 18 years of age or older who was born after 1956 should get at least one dose of MMR vaccine, unless they can show that they have either been vaccinated or had all three diseases.

MMR vaccine may be given at the same time as other vaccines.

Children between 1 and 12 years of age can get a "combination" vaccine called MMRV, which contains both MMR and varicella (chickenpox) vaccines. There is a separate Vaccine Information Statement for MMRV.

3 Some people should not get MMR vaccine or should wait.

- Anyone who has ever had a life-threatening allergic reaction to the antibiotic neomycin, or any other

Comment by Dr. James Lyons-Weiler and Bernadette Pajer

Re: Docket Number CDC-2016-0094
Proposed Revised Vaccine Information Materials for MMR (Measles, Mumps, and Rubella and MMRV (Measles, Mumps, Rubella, and Varicella) Vaccines
Federal Register October 18, 2016

Dec 15, 2016

We are providing this in response to the CDCs request for public comment.

Summary of our position: The proposed Vaccine Information Statements (VISs) do not provide to individuals sufficient information necessary for them to give fully informed consent, the legal agreement between an individual and a physician, first introduced by the Nuremberg Code, and outlined in the Canterbury decision of 1972, and subsequent rulings, regulations, and laws governing informed consent requirements. (HEALTH LAW: Informed Consent: What Must a Physician Disclose to a Patient? American Medical Association Journal of Ethics, July 2012, Volume 14, Number 7: 563-566.)

The steady erosion of informed consent by Congress and CDC in regards to vaccination reached a low point with the recent passage of 21st Century Cures Act which included unprecedented expansion of informed consent waivers and extension of product liability exemptions (sections 3024, 3091, 3092, 3093.) However, informed consent and other patient rights are still protected under other rules and regulations.

The efficacy and safety of Merck's MMR and MMRV vaccines are currently under intense scrutiny. Former Merck employees and virologists Stephen A. Krahling and Joan A. Wolchowski filed a suit against Merck in 2010, alleging fraud in vaccine testing (see complaint here). Merck delayed the trial for years, but the court has now ordered that discovery be completed by March 2017 (Former Merck Scientists Sue Merck Alleging MMR Vaccine Efficacy Fraud)

Further, CDC senior scientist Dr. William Thompson has filed for whistleblower status, presented 10,000 documents to Congressman Bill Posey, and confessed that the DeStefano et al. (2004) study, deleted positive association results between on-time vaccination w/MMR and autism diagnosis for both African American Male and for Isolated Autism subgroup analyses (Statement of William W. Thompson, Ph.D., Regarding the 2004 Article Examining the Possibility of a Relationship Between MMR Vaccine and Autism). The data removed from the study would support a causal link between the timing of the administration of the MMR vaccine and autism. Jason Chaffetz of the House Oversight Committee has begun investigating (Jason Chaffetz video speaking on CDC & Thompson investigation).

With the integrity, effectiveness, and safety of the MMR/MMR-V currently in question and the subject of much public controversy, revising the VIS's at this time is absolutely critical in order to inform the stakeholders that the effectiveness and safety are currently unknown and under investigation. The drafts presented here for consideration fail to mention this critical information.

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[redacted]

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The regulatory vacuum has led to rampant, perhaps willful, ignorance, as evidenced by such documents as the AAP's "Countering Vaccine Hesitancy" guide, with unsupported statements such as:

> *"The opposition to the presence of aluminum as an adjuvant in some vaccines can be addressed by providing evidence for both the necessity of the aluminum for a vigorous immune response and* ***the lack of evidence for its toxicity****."*

We encourage AAP, Congress, and CDC to read the literature on aluminum neurotoxicity:

https://www.ncbi.nlm.nih.gov/pubmed/?term=aluminum+neurotoxicity

Ignorance of the actual risks involved has also led to publication of an article by an academic individual in the New England Journal of Medicine contemplating the usefulness and best ways to **coerce** patients into accepting vaccines (Colgrove, 2016):

"Both persuasion and ***coercion*** *are necessary, and neither is sufficient. Laws serve as a critical safety net as well as a powerful symbolic statement of proimmunization social norms."*

[Colgrove J Vaccine Refusal Revisited - The Limits of Public Health Persuasion and Coercion. N Engl J Med. 2016 Oct 6;375(14):1316-1317.]

Coercion of patients into medical practices and experimentation has NOT been the accepted societal norm since the practices of Dr. Mengele, the Nazi doctor who tricked children into

Rebuttal to the comment by Dorit Reiss
By Dr. James Lyons-Weiler, PhD and Bernadette Pajer

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While we have provided our remarks on CDC's draft VIS revisions in a separate comment (Comment Tracking Number **1k0-8tlr-fn92**), we are providing this rebuttal in response to the comment of Dorit Reiss with deep concern on the incorrectness of some of her points. [redacted]

Ms. Reiss's comment can be found here: https://www.regulations.gov/document?D=CDC-2016-0094-0151

Rebuttal to the comment by Dorit Reiss
By Dr. James Lyons-Weiler, PhD and Bernadette Pajer

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While we have provided our remarks on CDC's draft VIS revisions in a separate comment (Comment Tracking Number **1k0-8tlr-fn92**), we are providing this rebuttal in response to the comment of Dorit Reiss with deep concern on the incorrectness of some of her points. Ms. Reiss is a professor at a school of law and as such her comments may be taken as fact by those who do not take the time to verify them. Unfortunately, many of her claims of fact are demonstrably incorrect. Her employer is affiliated with the University of California, which for many endeavors is in partnership with Kaiser Permanente, which in turn is in partnership with Merck, the manufacturer of MMR and MMRV. Ms. Reiss has elsewhere disclosed personal conflicts of interest via family ownership of stock in at least one vaccine-manufacturing company. While these types of affiliations and partnerships are not unusual and are not proof of influence, Ms. Reiss uniformly and very actively takes positions on vaccine law and policy that favor vaccine manufacturers and restrict medical freedom of choice. (http://www.uchastings.edu/faculty/reiss/)

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Further Redaction

- “Dr. William Thompson, one of the researchers on the DeStefano et al study, mentioned above, came forward in 2014 as a whistleblower on this study, stating results that did, in fact show a causal link between the timing of the administration of the MMR and autism were removed prior to presentation of the results to the IOM.”

(This study was one of the 17/22 rejected by the IOM, but was used to deny settlements for autism in the Omnibus hearings)

(3) Reiss claims:

> "The VIS both mentions "permanent brain damage" and "long term seizures" as "severe and very rare problems following MMR vaccines." However, recent studies do not support a link between MMR and encephalitis or brain damage, and to my knowledge, not to seizures, either. See: http://pediatrics.aappublications.org/content/early/2015/01/01/peds.2014-1822 "

Rebuttal: Ms. Reiss's citation disproves her claim:

> "BACKGROUND AND OBJECTIVES: All measles-containing vaccines are associated with several types of adverse events, including seizure, fever, and immune thrombocytopenia purpura (ITP). Because the measles-mumps-rubella-varicella (MMRV) vaccine compared with the separate measles-mumps-rubella (MMR) and varicella (MMR + V) vaccine **increases a toddler's risk for febrile seizures**, we investigated whether MMRV is riskier than MMR + V and whether either vaccine elevates the risk for additional safety outcomes." (emphasis added)

The study results showed:

> "Compared with MMR + V, MMRV **increased risk of seizure and fever 7 to 10 days after vaccination**." (emphasis added)

This was not a vaccinated verses non-vaccinated study; it was a study that only compared outcomes for those vaccinated with MMRV versus those vaccinated with MMR + V.

The regulatory vacuum has led to rampant, perhaps willful, ignorance, as evidenced by such documents as the AAP's "Countering Vaccine Hesitancy" guide, with unsupported statements such as:

> *"The opposition to the presence of aluminum as an adjuvant in some vaccines can be addressed by providing evidence for both the necessity of the aluminum for a vigorous immune response and* ***the lack of evidence for its toxicity****."*

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Coercion of patients into medical practices and experimentation has NOT been the accepted societal norm since the practices of Dr. Mengele, the Nazi doctor who tricked children into

Informed Consent

Required at two levels, every patient, every procedure:

(1) Acceptance of a medical procedure based on complete information on benefits & risks

(2) Participation in a clinical trial after being provided complete information on benefits & risks.

Most of the studies conducted on vaccine safety rely on post-marketing surveillance using weak "association studies" with data from passively collected data sources (such as VAERS). Patients are not informed that they, or their children are, in fact, participating in a large, shoddily-run, non-randomized retrospective clinical trial. This practice is widespread, and violates provisions of the National Research Act [Title II, Public Law 93-348], Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research [45 CFR 46] and revisions of various regulations, rules, and laws ([21 CFR 50, [21 CFR 56], [45 CFR 46 Subpart D], [10 CFR 745]. Pregnant women and fetuses are afforded special protections by [45 CFR 46 Subpart B], and children are afforded additional protections by [45 CFR 46 Subpart D]. Yet the rights of pregnant women and fetuses are violated with each and every vaccine administered to them because not only is there a paucity of pre-licensing clinical trials, no vaccine is actually licensed for use to protect fetuses, and pregnant women are not told any of this as they are pressured to get vaccinated. (FDA: Vaccines For Use in Pregnancy)

Of note, in the Common Federal Policy for the Protection of Human Subjects ("Common Rule") [10 CFR 745] Sec 745.103(b)(3), none of these rights were revoked by any subsequent legislation, including [21 CFR 50.24], which allows the relaxation of requirements for informed consent during emergencies. In fact the Common Rule re-asserted safeguards both for informed consent, and for special protections against coercion:

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Failure to Secure Informed Human Subject Research Consent

National Research Act [Title II, Public Law 93-348]

Regulations for the Protection of

Human Subjects of Biomedical and Behavioral Research [45 CFR 46] et sub

Revisions of various regulations, rules, and laws ([21 CFR 50, [21 CFR 56], [45 CFR 46 Subpart D], [10 CFR 745].

Pregnant women and fetuses are afforded special protections [45 CFR 46 Subpart B]

Children are afforded additional protections **[45 CFR 46 Subpart D]**.

The human rights of pregnant women and fetuses are violated with each and every vaccine administered to them because not only is there a paucity of pre-licensing clinical trials, no vaccine is actually licensed for use to protect fetuses, and pregnant women are not told any of this as they are pressured to get vaccinated.

“Common Rule” Disallows Coercion vs. [21 CFR 50.24] for Consent *altogether*

Common Federal Policy for the Protection of Human Subjects ("Common Rule")
[10 CFR 745] Sec 745.103(b)(3), none of these rights were revoked by any subsequent legislation, including [21 CFR 50.24], which allows the relaxation of requirements for informed consent during emergencies. In fact the Common Rule re-asserted safeguards both for informed consent, and for special protections against coercion:

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. ***An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.***

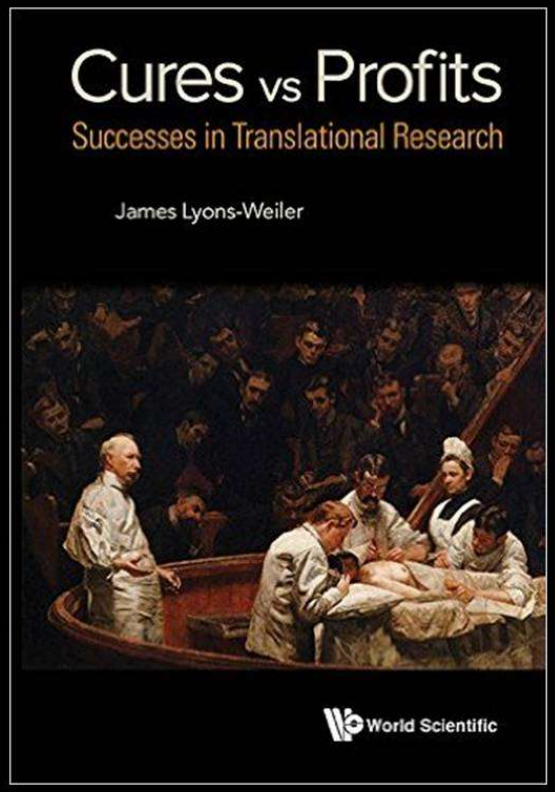
Common Rule (Cont.)

The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents ***from liability for negligence****.*

"When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects."

Scale of Injuries

- >$US 3Billion Paid out via Special Masters Court for vaccine injuries
- Supreme Court ruled vaccines “unavoidably unsafe”
- Vaccine Court has limited recognition of vaccine injuries, allowing encephalopathy, specifically excluding “autism”



Available at Amazon.com

Excerpt from "Cures vs. Profits":

Why would the CDC publish such as page in 2014, a full ten years after the study?

In 2014, one of the authors of the CDC study, Dr. William Thompson, Ph.D., was recorded by one Dr. Hooker. Dr. Hooker had allegedly spent 10 years since the CDC study petitioning for access to the entire data behind the study.

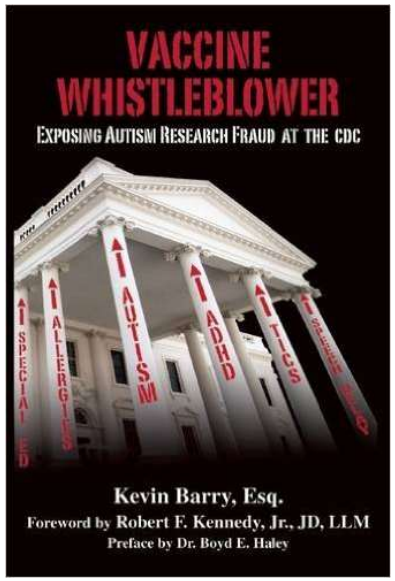
In the interview, Dr. William Thompson is heard making the following statements:

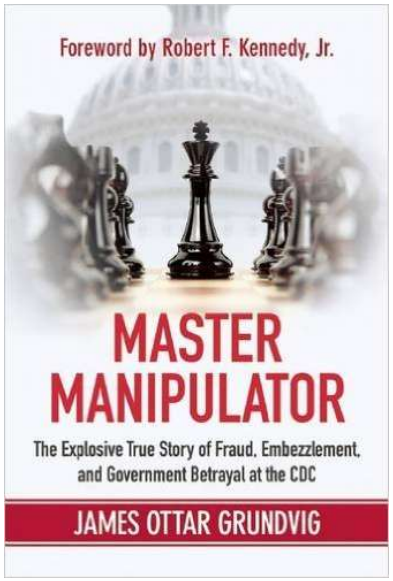
"Oh my God, I cannot believe we did what we did. But we did. It's all there."
"The higher-ups wanted to do certain things and I went along with it."
"It was the lowest point in my career that I went along with that paper. And I went along with this, and didn't report significant findings"
"I have great shame now when I meet families with kids with autism because I've - I've been part of the problem."

CDC Whistleblower Dr. William Thompson

- Hired Whistleblower lawyer re-asserting that YES, they removed results
- Was suspended prior to the IOM report for informing then-director Julie Gerberding

- My independent analyses of reveal many repeated instances of
  - Analysis-to-result
  - Changes to study design
  - Wrongful exclusion
  - Model overfit
  - Obvious misinterpretation





Typical Moderate or Serious Adverse Event Experience

“It is common practice for office staff to reassure parents over the phone that a vaccine reaction is normal, expected, and not any cause for concern. They generally recommend Tylenol for the pain and fever, but won't advise an in-person medical evaluation. This may be proper procedure for mild reactions like fussiness, moderate fever, and mild swelling and redness at the injection site. But all moderate to severe reactions, like hives, lethargy, seizures, fever of 105 degrees, or inconsolable crying lasting 3 hours or more (encephalitis), warrant prompt in-person medical attention.”

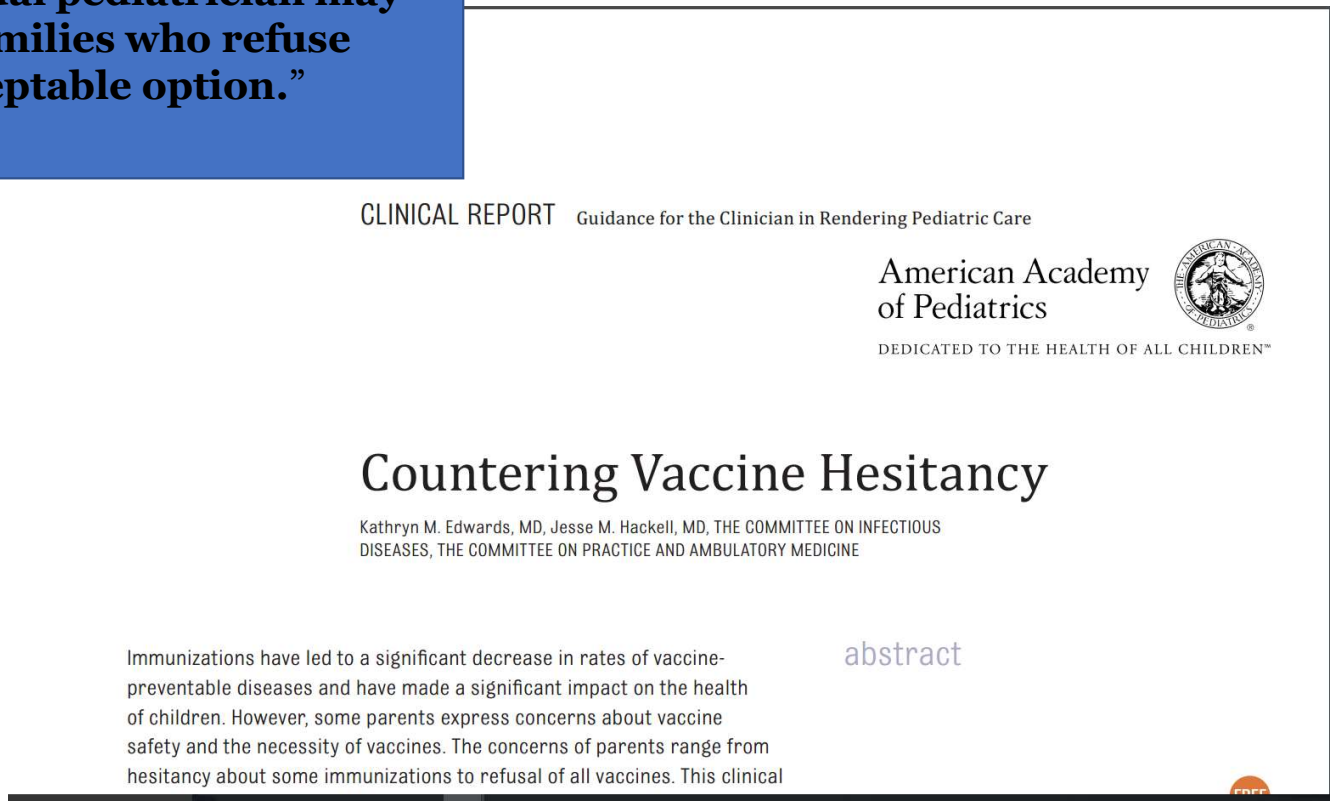
Encroachments

- Product mislabeling
- Possible fraud (Merck)
- Failure to consider all of the science (CDC)
- Denial of Informed Consent (2 levels)
  - Changing conversation from risk to efficacy
  - 21st Century Cures Act
- Overt calls for **coercion**
- Denial of rights to public services
- Denial of access to medical care
- Job Loss
- Overt calls for Denial of 1st Amendment Rights
- Censorship of American Citizens

Implications of the "Recipe"

- A large component of consumer demand for flu vaccination is contingent upon things we can't control (e.g., timing, severity, extent, duration of the disease and resulting illness).
- Fostering demand, particularly among people who don't routinely receive an annual influenza vaccination, requires creating concern, anxiety, and worry. For example:
  - A perception or sense that many people are falling ill;
  - A perception or sense that many people are experiencing bad illness;
  - A perception or sense of vulnerability to contracting and experiencing bad illness.

"The decision to dismiss a family who continues to refuse immunization is not one that should be made lightly, nor should it be made without considering and respecting the reasons for the parents' point of view," the report states. "**Nevertheless, the individual pediatrician may consider dismissal of families who refuse vaccination as an acceptable option.**"



CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

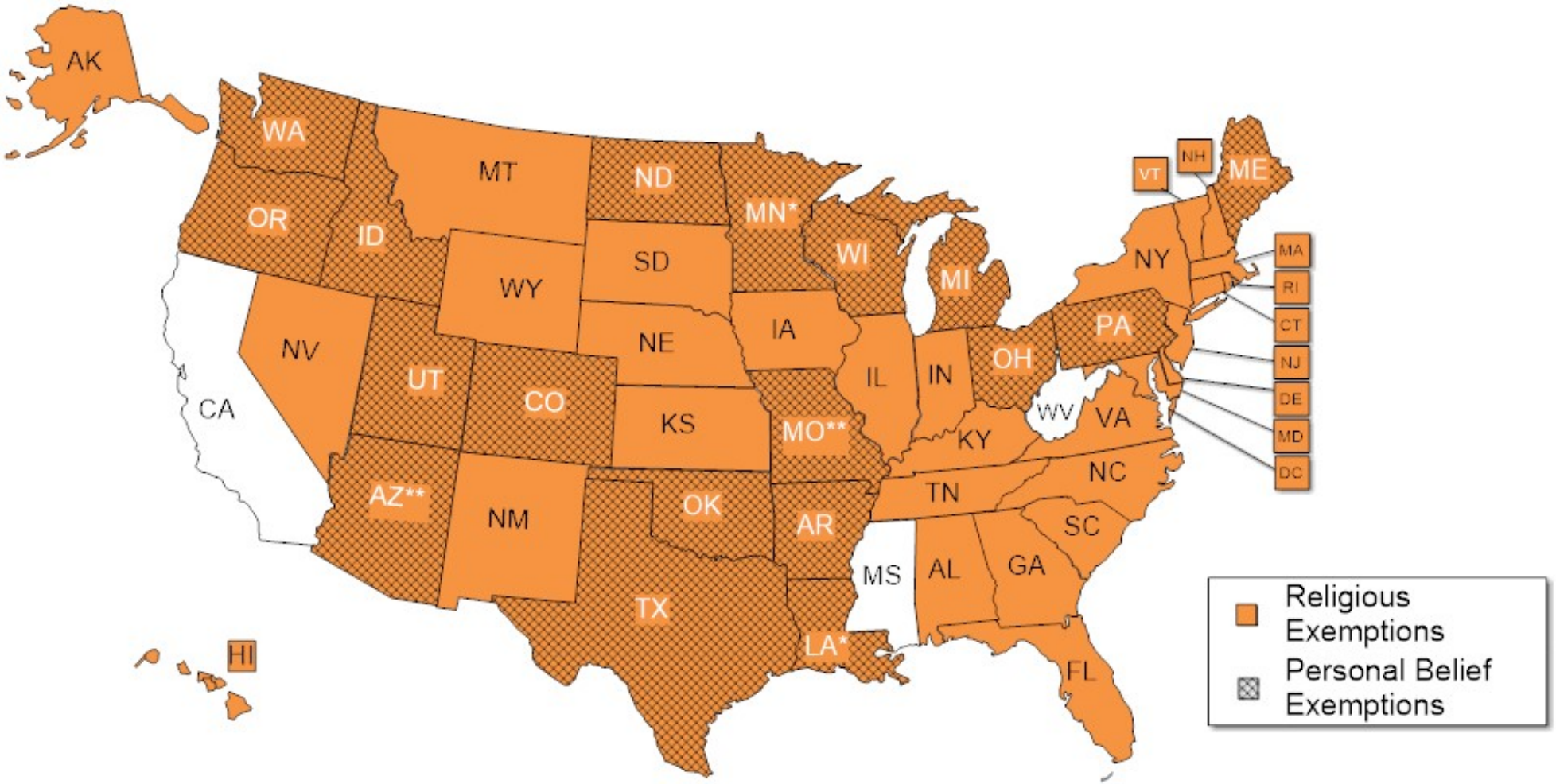
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Countering Vaccine Hesitancy

Kathryn M. Edwards, MD, Jesse M. Hackell, MD, THE COMMITTEE ON INFECTIOUS DISEASES, THE COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE

abstract

Immunizations have led to a significant decrease in rates of vaccine-preventable diseases and have made a significant impact on the health of children. However, some parents express concerns about vaccine safety and the necessity of vaccines. The concerns of parents range from hesitancy about some immunizations to refusal of all vaccines. This clinical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VA
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
DC
Religious Exemptions
Personal Belief Exemptions

Rules and Regulations on Informed Consent

- Nuremberg Code, and outlined in the Canterbury decision of 1972, and subsequent rulings, regulations, and laws governing informed consent requirements. (HEALTH LAW: Informed Consent: What Must a Physician Disclose to a Patient? American Medical Association Journal of Ethics, July 2012, Volume 14, Number 7: 563-566.)

Coercion? Revocation of First Amendment Rights? USA? 2016? Really?

- Ignorance of the actual risks involved has also led to publication of an article by an academic individual in the New England Journal of Medicine contemplating the usefulness and best ways to **coerce** patients into accepting vaccines (Colgrove, 2016):

- *"Both persuasion and **coercion** are necessary, and neither is sufficient. Laws serve as a critical safety net as well as a powerful symbolic statement of proimmunization social norms."*

- [Colgrove J Vaccine Refusal Revisited - The Limits of Public Health Persuasion and Coercion. N Engl J Med. 2016 Oct 6;375(14):1316-1317.]

Holland, M. 2015. Legally Censoring Speech on Vaccines and Autism: A Response. www.jurist.org/forum/2015/12/mary-holland-vaccines-autism.php

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ACADEMIC COMMENTARY OP-EDS ON LEGAL NEWS BY LAW PROFESSORS AND JURIST SPECIAL GUESTS

Legally Censoring Speech on Vaccines and Autism: A Response

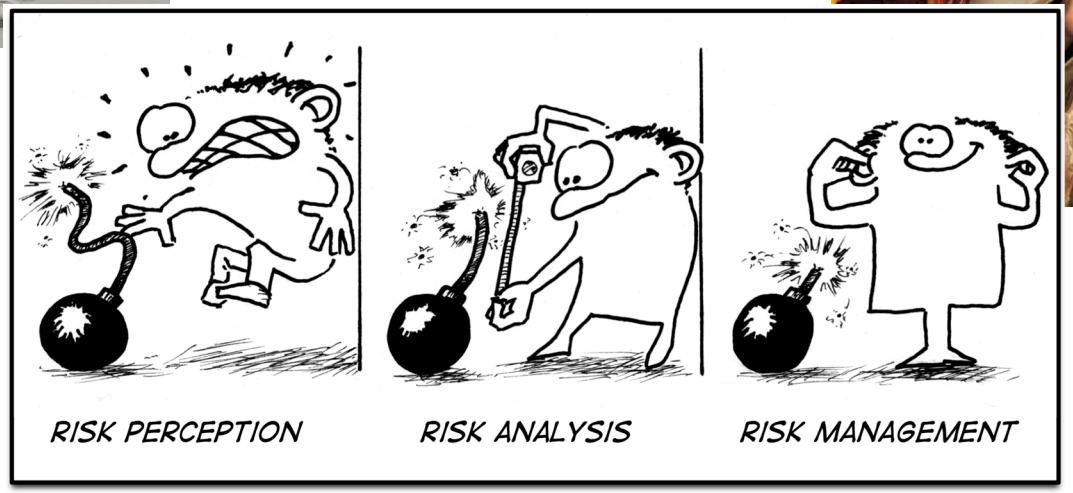
Friday 11 December 2015 at 8:52 AM ET

edited by Maria Coladonato

JURIST Guest Columnist Mary S. Holland from the New York University School of Law discusses the legality of censoring speech on vaccines and autism...

In a recent guest column, Professors James C. Hodge, Jr. and Doug Campos

Manipulation of the Perception of Risk without Actually Minimizing Risk



Review and Challenges…

- Autism is no more than 50% genetic, and at least 50% environmental
- Vaccines contribute to total load, and contribute to mitopathies, channelopathies, chronic microglial activation, encephalopathy, and many NDs, including autism.
- **Research is needed on causes of increased CNVs.**
- **Either/or thinking is not helpful. Think Synergy + Interactions.**
- Vaccines **must** be made more safe: **Ethical Vaccinomics.**

- Cost of vaccines in terms of NDs and lifelong suffering and death are not sufficiently determined
- **Coercion, and attempts to use the law to silence the minority viewpoint are the tools of tyrants, and have no place in our society.**

Challenges

- Need to re-cast research on neurodevelopment disorders completely
  - -it's not 'in their heads'
  - behavioral intervention **alone** will only frustrate
  - genetic information can guide (Genes MATTER)
  - Diet and supplements MATTER
  - Environmental exposures MATTER
  - Vaccines MATTER
  - Detoxifying Kids MATTERS

- Recognize that **Vaccine risk denialism**
  - **Reduces** vaccine uptake
  - Hurts children (has been preventing prevention)
  - **Has prevented research on interventions**
  - Polarizes society
  - Pits pediatricians against parents
  - Protects major income streams – **for now**

*Abdominal pain/cramps * Allergic reaction *Allergies *Alzheimer's *Anaphylaxis *Angina *Apnea *Arthralgia *Arthritis *Aseptic meningitis *Asthma *Atopic dermatitis *Attention Deficit Disorder(A.D.D) * Attention Deficit Hyperactivity Disorder (ADHD) *Autism Spectrum *Autoimmune Disease *Bell's Palsy *Bipolar disease *Blindness *Bowel Problems *Brain Damage *Brain Inflammation *Bulging Fontanel *Cancer *Cardiac Distress *Cardiomypathy *Cerebral hemorrhage *Cerebral palsy *Chicken pox *Chills *Chronic Fatigue Syndrome *Collapse/ Shock *Coma *Confusion *Congestive Heart Failure *Conjunctivitis *Constipation *Convulsions *Coughing *Crohn & Rsquo's Disease *Cystitis *Deafness *DEATH *Dementia *Demyelization *Development Delay *Diabetes *Diarrhea *Dizziness *Throbbing in Ear *Earache *Eczema *Eczema Vaccinatium *Encephalitis *Encephalomyelitis *Encephalopathy *Epilepsy *Erythema *Multiform Fatigue *Fever *Fibromyalgia *Flu * Guillain barre syndrome (GBS) *Gulf War Syndrome *Hallucinations *Headache *Heart attack *Hemolytic anemia *Herpes Zoster *Hib Disease *High Blood Pressure *High-Pitched Screaming *Hives *Hyperactivity *Hypotension *Hypotonic/ Hypo responsive Immune system problems *Indurations *Inflammatory Bowl Disease *Influenza accidental/inadevent *Insomnia *Intussusceptions *Irritability *Itching (prurtis) *Jaundice *Joint Pain *Learning Disabilities *Lethargy *Liver Damage *Loss of Appetite *Loss of Eye Contact *Loss of Speech *Lupus *Malaise *Measles *Memory Loss *Mercury Poison *Mesothelioma *Moneuropathy *Multiple Sclerosis *Mumps *Muscle Aches *Myopericarditis *Nausea *Neurological Damage *Neuropathy *Nodules *Optic Neuritis *Orchitis *Otitis *Media(inner ear infection) *Pain at Injection Site (unusual or prolonged) *Paralysis *Pervasive Development Disorder (P.D.D) *Polio *Polyneuropathy *Prolonged Crying *Psychotic Behavior *Radiculoneuritis *Rash *Redness at the Injection Site *Regression *Respiratory Distress *Respiratory Infection *Retinal Hemorrhage *Retinitis *Rhinitis

Disease *Cystitis *Deafness *DEATH *Dementia *Demyelization *Development Delay
*Diabetes *Diarrhea *Dizziness *Throbbing in Ear *Earache *Eczema *Eczema
Vaccinatium *Encephalitis *Encephalomyelitis *Encephalopathy *Epilepsy *Erythema
*Multiform Fatigue *Fever *Fibromyalgia *Flu * Guillain barre syndrome (GBS) *Gulf
War Syndrome *Hallucinations *Headache *Heart attack *Hemolytic anemia *Herpes
Zoster *Hib Disease *High Blood Pressure *High-Pitched Screaming *Hives
*Hyperactivity *Hypotension *Hypotonic/ Hypo responsive Immune system problems
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*Intussusceptions *Irritability *Itching (prurtis) *Jaundice *Joint Pain *Learning
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Speech *Lupus *Malaise *Measles *Memory Loss *Mercury Poison *Mesothelio
*Moneuropathy *Multiple Sclerosis *Mumps *Muscle Aches *Myopericarditis *
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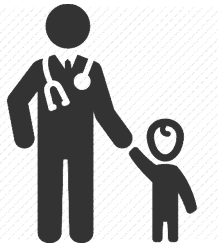
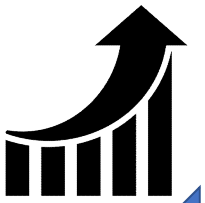
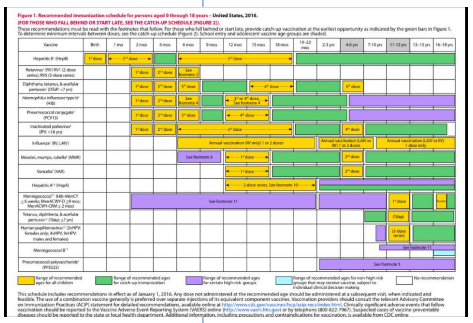
*Psychotic Behavior *Radiculoneuritis *Rash *Redness at the Injection Site *Re
*Respiratory Distress *Respiratory Infection *Retinal Hemorrhage *Retinitis *Rh
*Rosella *Rubella *Sensory Processing Disorder (SPD) *Schizophrenia *Screaming
*Seizure *Seizure Disorder *Sepsis *Shaken Baby Syndrome (SBS) *Sudden Infant Death
Syndrome (SIDS) *Shingles *Shock *Shortness of Breath *Skin Disorders *Sleepiness
*Small pox *Sore arms *Sore throat *Stiff neck *Stroke *Sub acute Sclerosing Pain *SV-
40 related Cancer *Sweating *Swelling at the Injection Site *Swollen Lymph Nodes
*Tenderness, localized *Thrombocytopenia *Transverse myelitis *Urticarnia *Vaccinia
*Violent Behavior *Vomiting *Weakness

Vaccine Risk Awareness 2017

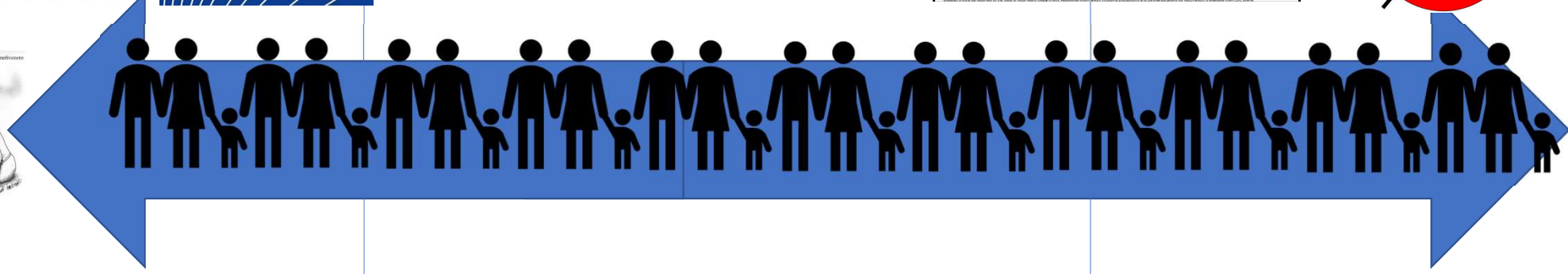


Marketing





“Anti-Vax”
“Refusniks”

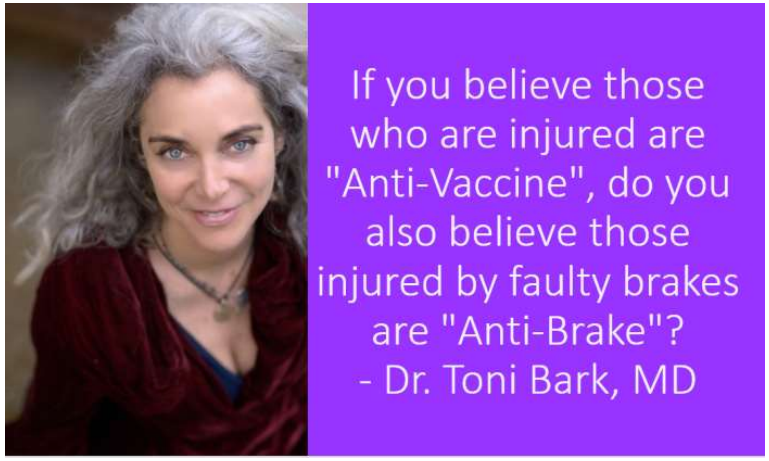


MEDICAL EXEMPTIONS…. WAIVERS… RIGHTS TO INFORMED CONSENT…

A Media Guide to Vaccine Risk Awareness

- **Anti-vax: "I want to ban all vaccines. Vaccines can never be made safer."**

- **VRA: "Vaccine risk is real, and should be minimized."**



THE JOURNAL OF PEDIATRICS • www.jpeds.com COMMENTARY

Professional Responsibility and Early Childhood Vaccination

Frank A. Chervenak, MD[1], Laurence B. McCullough, PhD[2], and Robert L. Brent, MD, PhD, DSc (Hon)[3]

The recent outbreaks of measles and other childhood infectious diseases in the US and other countries[1-3] have garnered considerable public attention and prompted controversy about early childhood vaccination.[4,5] A newcomer to this controversy would be forgiven for thinking that there is a scientific and ethical basis for controversy about the professional responsibilities of physicians regarding early childhood vaccination. For example, there are reports of physicians stating publicly that they have not authorized vaccination of their own children.[6] At least 1 physician who holds federal elected office and is an announced Republican Party candidate for the nomination to become president of the US, Senator Rand Paul of Kentucky, has stated that parents' refusals of vaccination should be respected by physicians and the government.[4] Andrew Wakefield, a former physician who has been eliminated from the General Register in the United Kingdom, fabricated data supporting a connection of the measles vaccine to autism, in a paper that was formally withdrawn.[4,7,8]

The safety and effectiveness of early childhood vaccination are well established.[9-13] In response to the recent measles outbreak, the American Academy of Pediatrics has recently released a statement urging parents to have their children vaccinated.[14] In this article, using the professional responsibility model of pediatric ethics, we address the ethics of early childhood vaccination, including counseling parents, the

standard, a beneficence-based core component of pediatric ethics.[18] This standard can function as an ideal or as a norm.[19] As an ideal, it sets a goal toward which pediatricians

Parental Refusal of Childhood Vaccines and Medical Neglect Laws

Efthimios Parasidis, JD, MBioethics, and Douglas J. Opel, MD, MPH

Objectives. To examine the relation of vaccine refusal and medical neglect under child welfare laws.

Methods. We used the Westlaw legal database to search court opinions from 1905 to 2016 and identified cases in which vaccine refusal was the sole or a primary reason in a neglect proceeding. We also delineated if religious or philosophical exemptions from required school immunizations were available at the time of adjudication.

Results. Our search yielded 9 cases from 5 states. Most courts (7 of 9) considered vaccine refusal to constitute neglect. In the 4 cases decided in jurisdictions that permitted religious exemptions, courts either found that vaccine refusal did not constitute neglect or considered it neglect only in the absence of a sincere religious objection to vaccination.

Conclusions. Some states have a legal precedent for considering parental vaccine refusal as medical neglect, but this is based on a small number of cases. Each state should clarify whether, under its laws, vaccine refusal constitutes medical neglect. (*Am J Public Health.* 2017;107:68–71. doi:10.2105/AJPH.2016.303500)

Parental refusal of childhood vaccines is a contentious issue in pediatrics and

result in harm to the child) constitute child maltreatment.

reports solely based on failure to vaccinate,[6] and Michigan has an explicit policy to this effect.[7] A few states codify that vaccine refusal regardless of reason,[8] or solely for sincere religious beliefs,[9] does not constitute medical neglect. Furthermore, even if vaccine refusal amounts to medical neglect, it is not clear that this finding requires state intervention. Ross and Aspinwall[10] contend that there should be a distinction between medical neglect and state intervention, arguing that vaccine refusal constitutes the former but does not warrant the latter. Chervenak et al.[4] argue that the purpose of reporting parents who refuse childhood vaccines to CPS for neglect is not to provoke "highly intrusive measures," such as loss of custody, but to "engage [CPS] in further efforts to persuade the parents."(p308) Simply invoking CPS, however, may undermine parents' views of

Contempt for Safety, or Blinded by Profits?

- Pharma: >$30Billion/year from vaccines – no liability for faulty products
- Media: DTC Marketing #1 source of revenue
- Medical establishment

Genetically Susceptible Subgroup(s)

- Individual risk
- Identifiable risk

By SHARYL ATTKISSON / CBS NEWS / May 12, 2008, 5:09 PM

The "Open Question" On Vaccines and Autism

2 Comments / Share / Tweet / Stumble / Email

2008

(CBS)

*Sharyl Attkisson is an investigative correspondent for **CBS News**.*

Perhaps the most puzzling thing about autism and ADD is that more than a decade into this public health crisis, our best, smartest government scientists and public health officials still say they have no idea what's causing it. Scary stuff, when parents having a child today realize there's at least an estimated 1 in 150 chance their child will have an autism disorder (1 in 90 if it's a boy).

While the government has been utterly unable to stop it, or even tell us what is causing it, they say they do know one thing: it's not vaccines. But today, in an exclusive interview with **CBS News**, Dr. Bernadine Healy becomes the most well-known medical voice yet to counter the government on that claim.

Sharyl Attkisson (2008) on Healy:

- The more she dug, she says, the more she came to believe the government and medical establishment were intentionally avoiding the question because they were afraid of the answer.
- Why? Healy says some in the government make the mistake of treating vaccines as an all-or-nothing proposition. The argument goes something like this: everybody gets vaccinated at the same time with the same vaccines or nobody will get vaccinated and long-gone deadly diseases will re-emerge. (When I asked about cases of brain damage resulting in autism that have been quietly compensated by the government in vaccine court over the years[3], one government official recently told me that "it's still better overall to get vaccinated than not to get vaccinated.")
- Healy says the argument need not be framed in those terms (vaccinate or don't vaccinate). Instead, she says, we should vaccinate, but work to do it in the safest manner possible based on what we know and what we can find out.

The Future of Artificial Immunization

- Screen for **unsafe** epitopes
- Use **more** antigen
- Use far less, or NO aluminum or mercury
- Deliver to the proper tissue
  - to activate dendritic cells
- RCT's, not correlation studies
- Compare Schedules
- **Actively** track, report, study injuries

Genetically Susceptible Subgroup

- Individual risk
- Identifiable risk

NEURODEVELOPMENT

RESEARCH

REFORM

2017

Neurodevelopment Research 2017+

Program 1. Neurodevelopmental Treatment, Therapy and Prognosis (NTTP)

Program 2. Neurodevelopmental Biomarkers of Patient-Specific Risk (NSRB)

Program 3. Neurodevelopmental Differential and Integrative Diagnosis (NDIDB)

Program 4. Neurodevelopmental Predictive Medicine Analysis (NPMA)

Program 5. Medico-Education of Neurodivergent Americans (MENA)

Program 6. Medical Education Vaccine Training Reform (MEVTR)

Program 7. Neurodevelopmental Philosophy and Bioethics (NPAB)

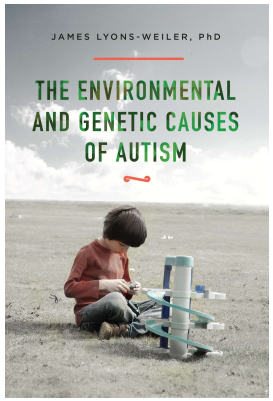
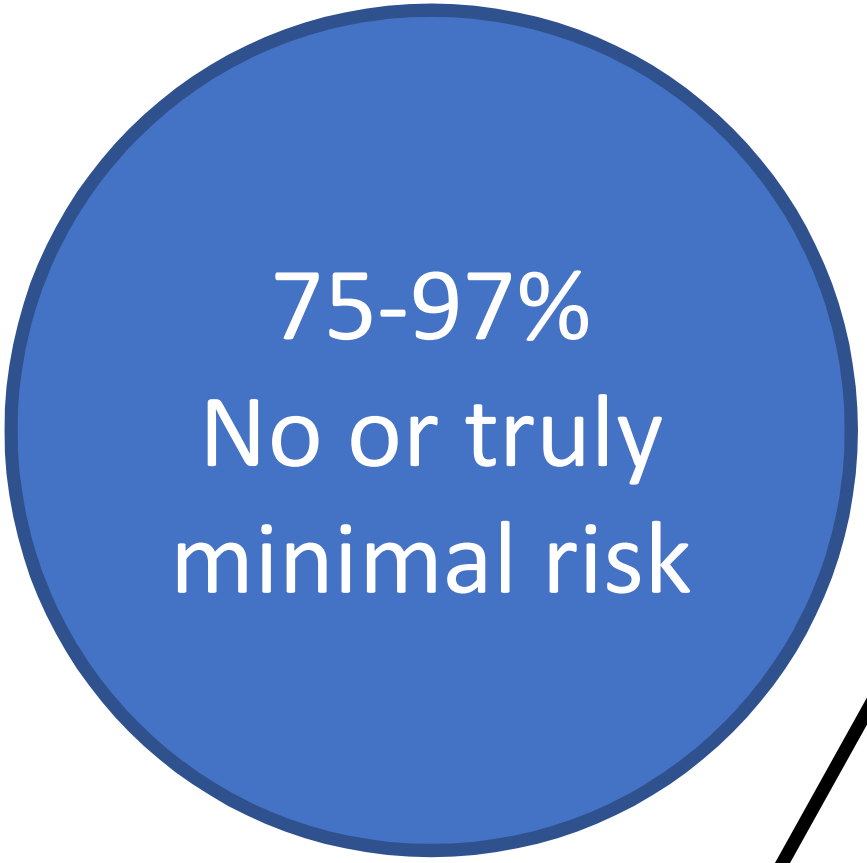


TABLE 4. EXAMPLES OF POSSIBLE FUTURE TREATMENTS OF AUTISM BY PHENOTYPE

Phenotype	Treatment
Aggression	Aripiprazole
Gastrointestinal	Fecal matter transplants, vancomycin
Language delay/loss	Adenosine receptor agonists
Microglial activation	Amantadine, luteolin, cannabinoids, many others
Renal peptiduria	Vitamin E, selenium
Repetitive Motor	Fluoxetine,[a] risperidone,[b] adenosine receptor agonists[c]
Seizures	Carbamazepine, ketogenic diet
Social	Oxytocin, tetrahydrobiopterin (cofactor BH4)

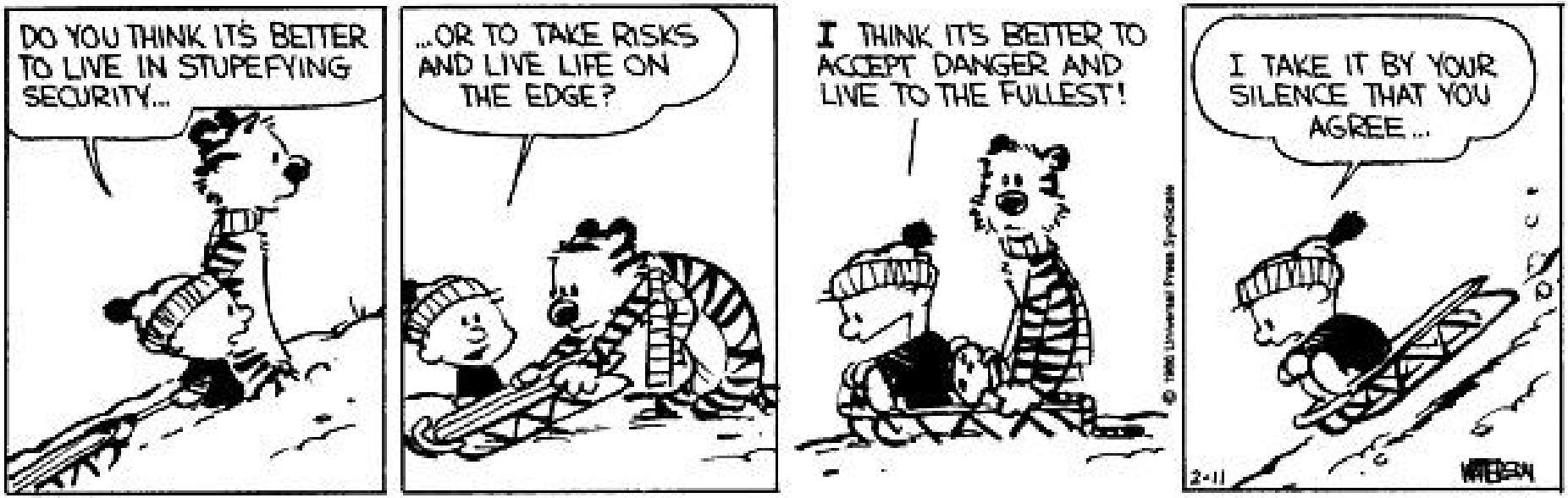
Gene-Directed Treatment Examples	
Mitochondrial dysfunction	Carnitine, various drugs
SCN1A (serotonin)	Clonazepam (microdoses)

Legal Issue: Equal Protection??



IDENTIFIABLE (Biomarkers)

WE CAN DO BETTER!


DO YOU THINK IT'S BETTER TO LIVE IN STUPEFYING SECURITY...
...OR TO TAKE RISKS AND LIVE LIFE ON THE EDGE?
I THINK IT'S BETTER TO ACCEPT DANGER AND LIVE TO THE FULLEST!
I TAKE IT BY YOUR SILENCE THAT YOU AGREE...
2-11
WATTERSON

Citations

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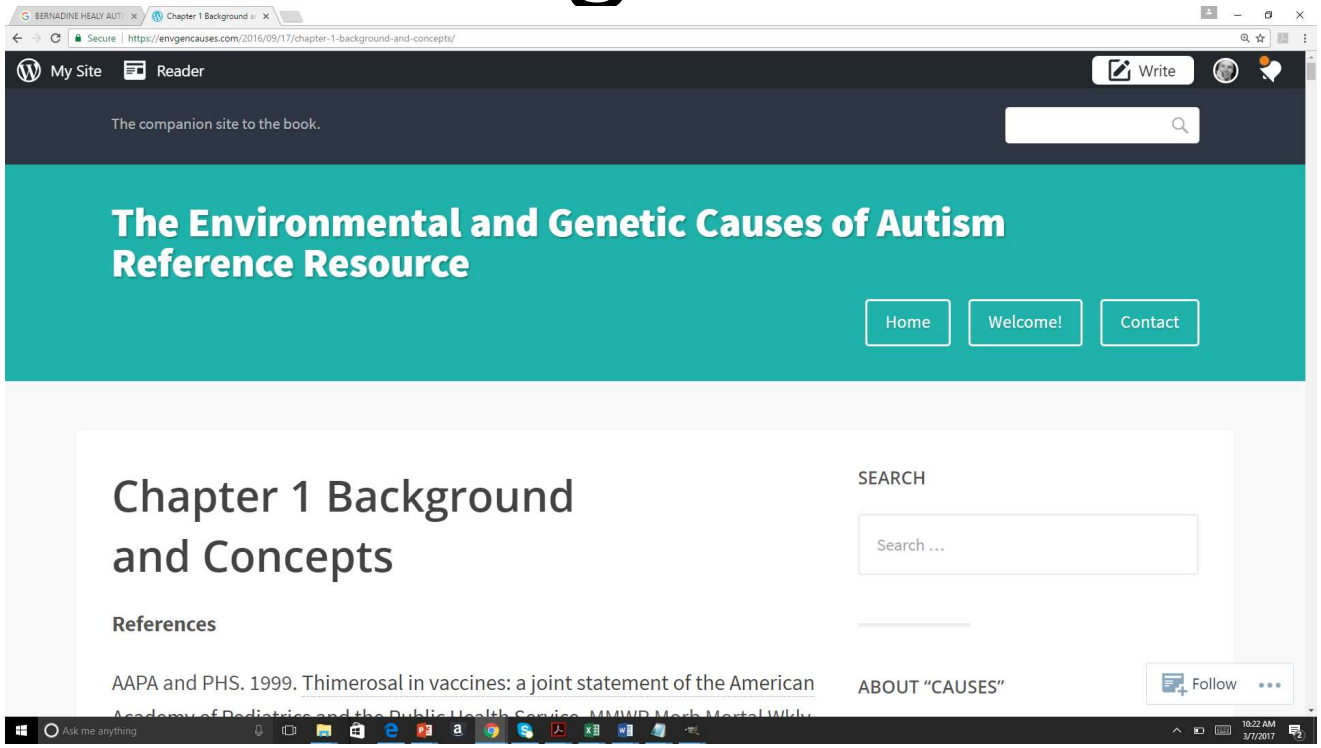
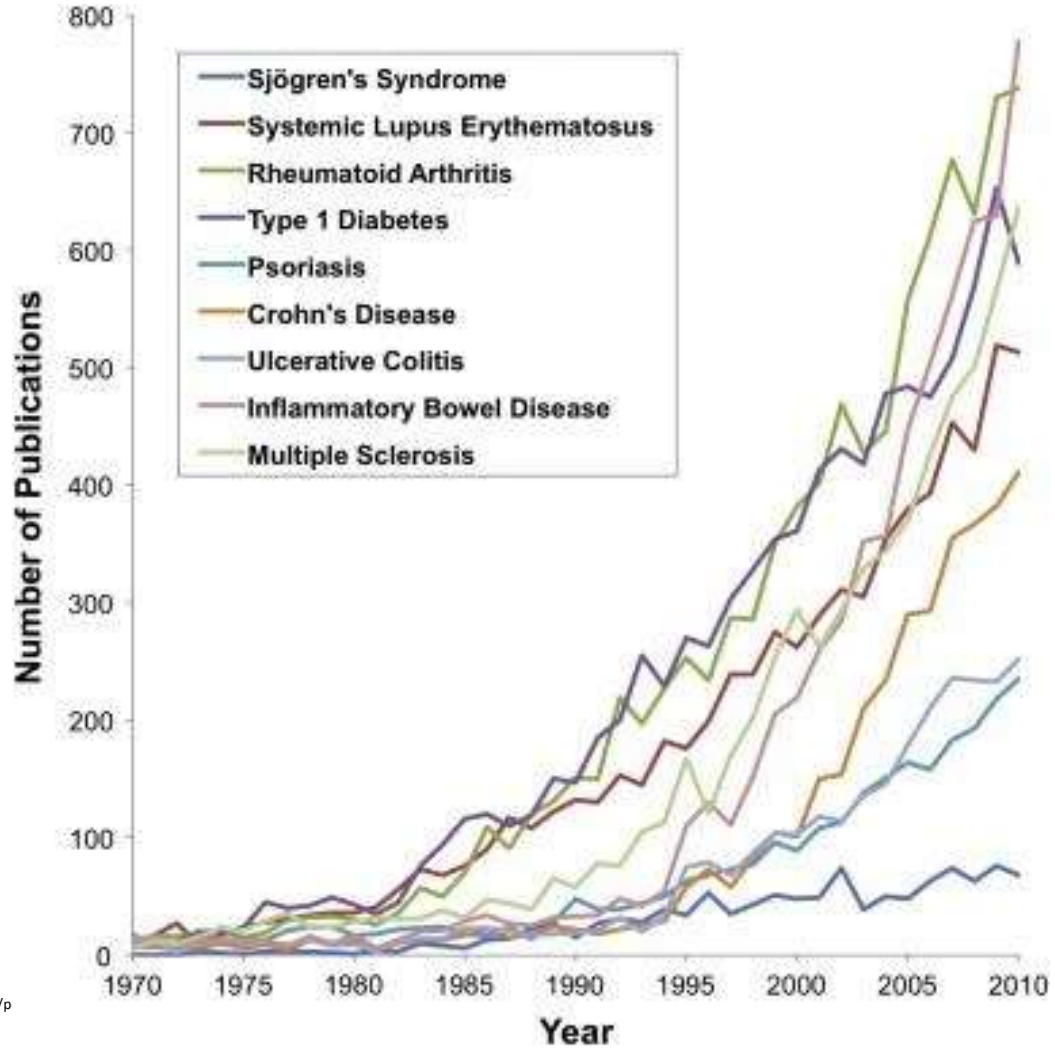
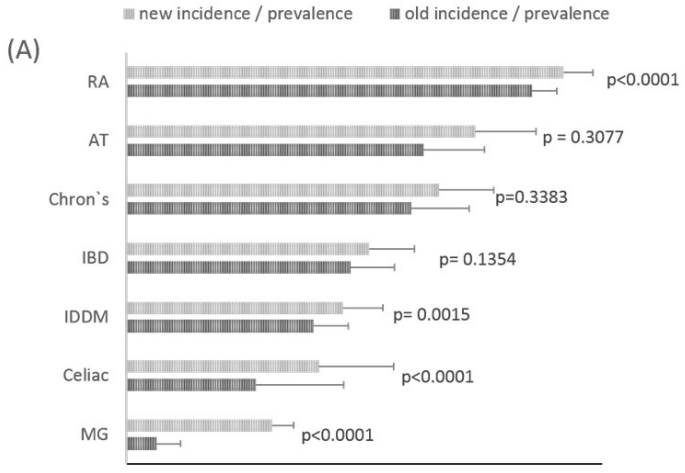




https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3518871/p

Figure 3. (A) Old vs. New surveys of incidence/prevalence of various autoimmune diseases. (B) The list of various diseases in specific countries and the years' ranges

(A)



(B)

Disease	Countries	Survey
RA	Canada	1995-2010
AT	Brazil, Denmark	1992-2012
Chron`s	Sweden, USA	1991-2007
IBD	Canada	1994-2005
IDDM	Canada, Israel, Serbia, Europe	1982-2010
Celiac	Canada, Denmark, Finland, Israel, Netherlands, USA, Sweden, UK, Czech Republic, Scotland, Spain, Estonia, New Zealand	1950-2011
MG	Denmark, Norway, Italy, Japan	1950-2006

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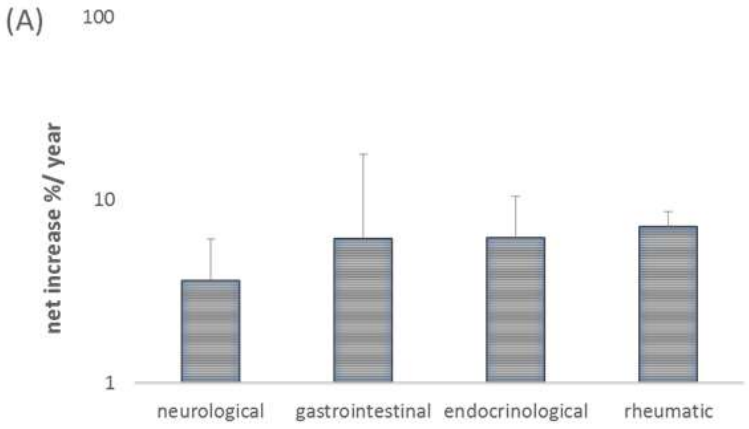
Figure 2. (A) The net %/year increases of diseases' categories. (B) The table below is detailing the different diseases and countries surveyed

(A)



(B)

disease kind	statistical significance (p; old vs. new)	Mean net increase %/year	countries	diseases
neurological	<0.0001	3.7 ±2.5	Finland, Denmark, Norway, Italy, Spain	MS, Myasthenia Gravis
gastrointestinal	<0.0001	6.2 ±11.5	Denmark, Canada, Sweden, USA, Finland, Israel, Netherlands, UK, Czech, Scotland, Spain, Estonia, New Zealand	Autoimmune Hepatitis, IBD, Chron`s, Celiac Disease
endocrinological	0.02	6.3 ±4.2	Brazil, Canada, Israel, Serbia, Europe	Autoimmune thyroiditis, IDDM
rheumatic	0.02	7.14 ± 1.5	Canada, UK	SARD, RA, SLE

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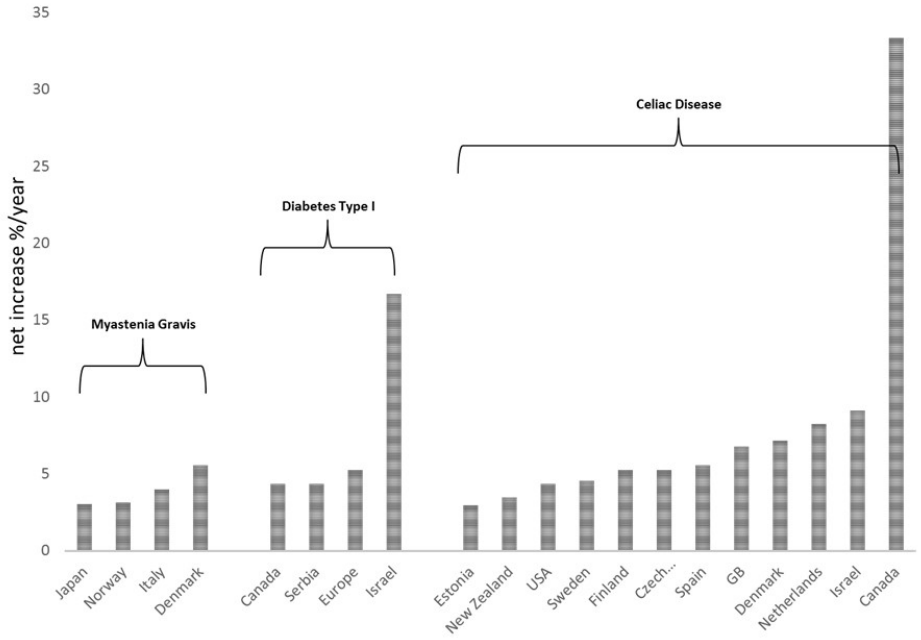
Figure 4. The net increase %/year of 3 autoimmune diseases in the surveyed countries



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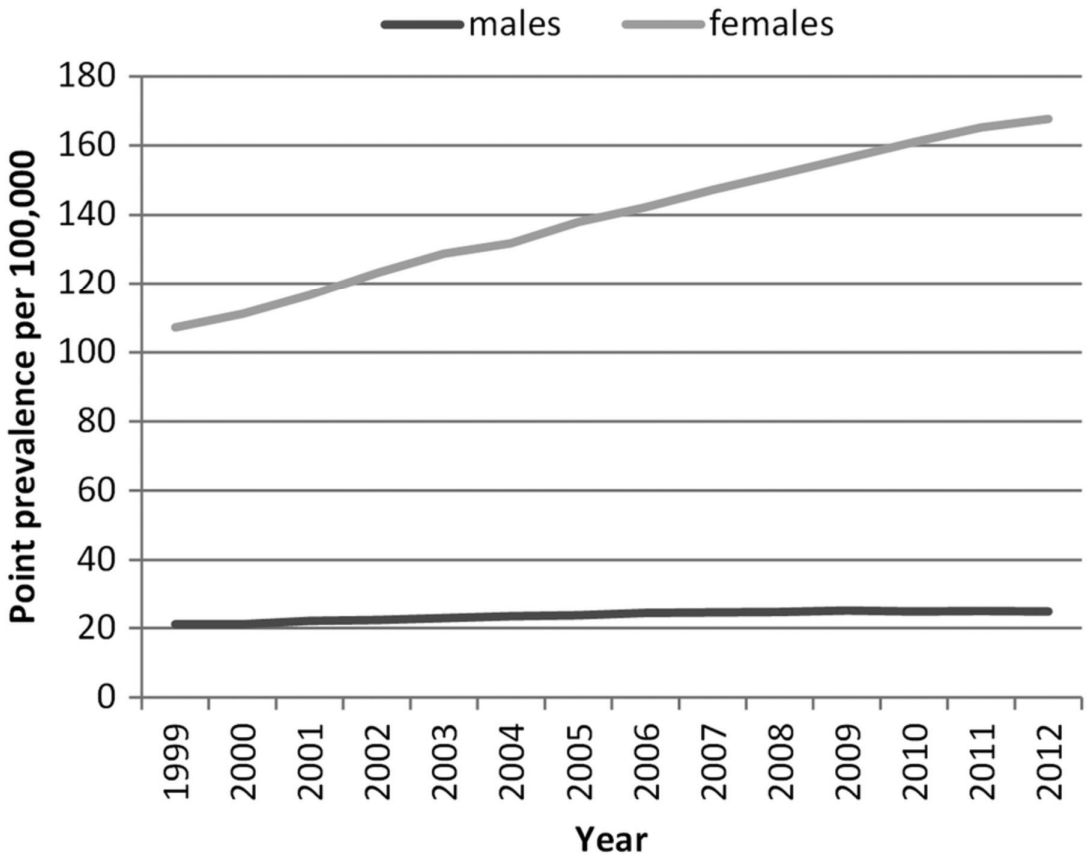
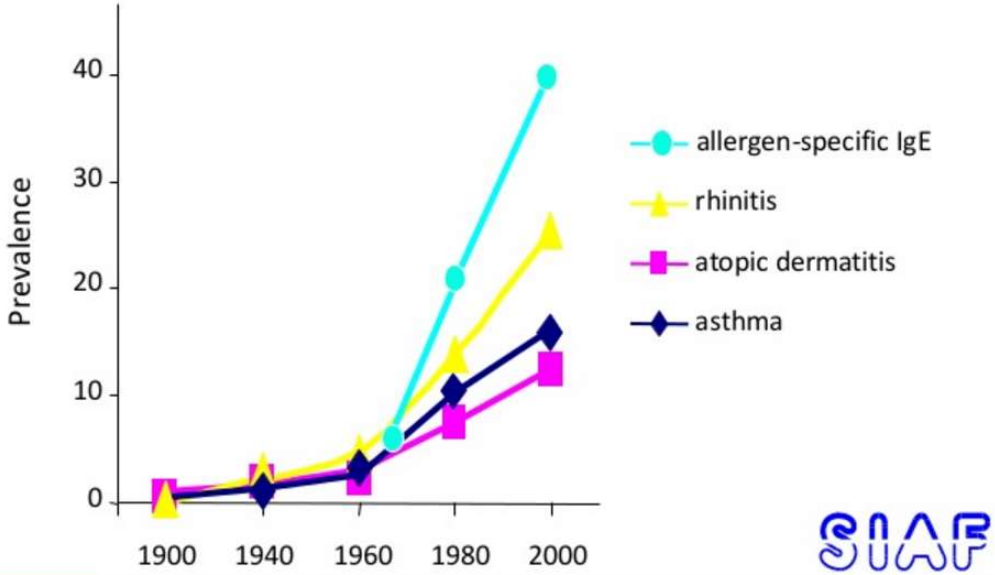
Annual systemic lupus erythematosus prevalence by gender.



Frances Rees et al. Ann Rheum Dis
doi:10.1136/annrheumdis-2014-206334

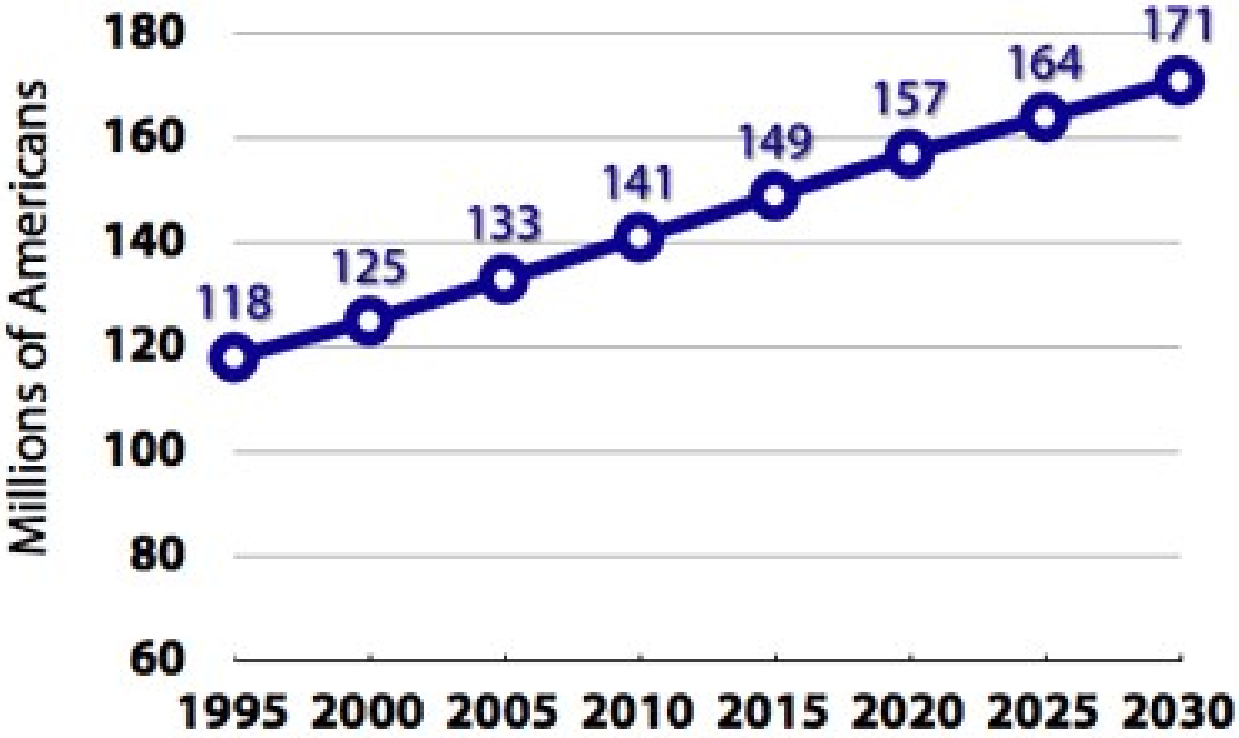
TheAllergy-Epidemic

Cezmi A Akdis (Swiss Institute of Allergy and Asthma Research)



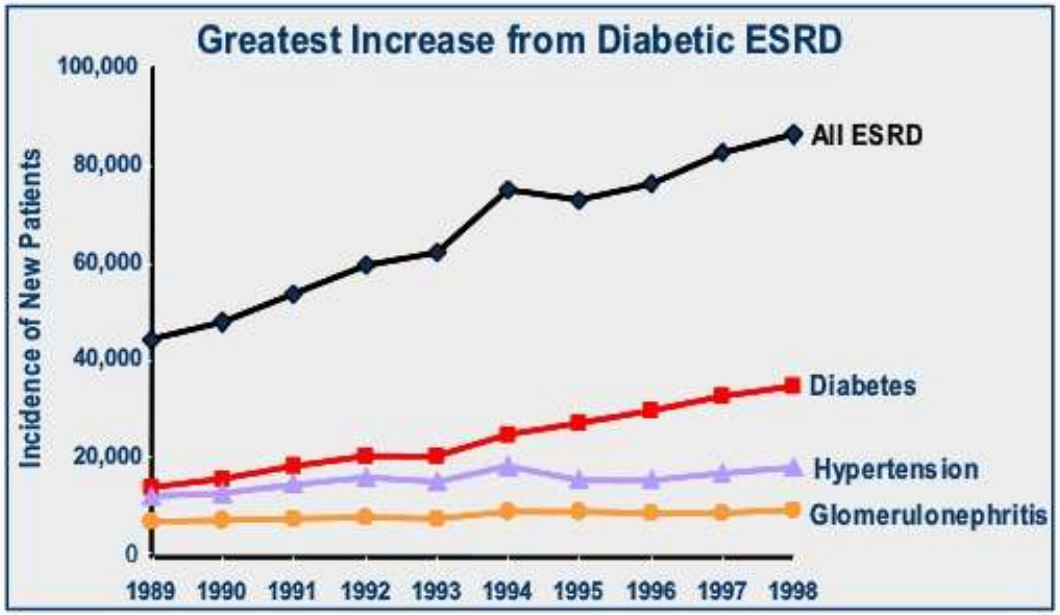
Allergy Asthma and One Health „The size of the problem"

Prevalence of Chronic Disease in the U.S.



Source: Wu, Shin-Yi *et al*. 2000. Projection of Chronic Illness Prevalence and Cost Inflation. RAND Corporation.

ESRD: ↑ Incidence and Prevalence



Diabetes is the most common cause in Caucasians, Hispanics, Asians, and overall. Among African-Americans, hypertension is the most common cause of ESRD.

US Renal Data System, 2000 Atlas of ESRD in the United States.

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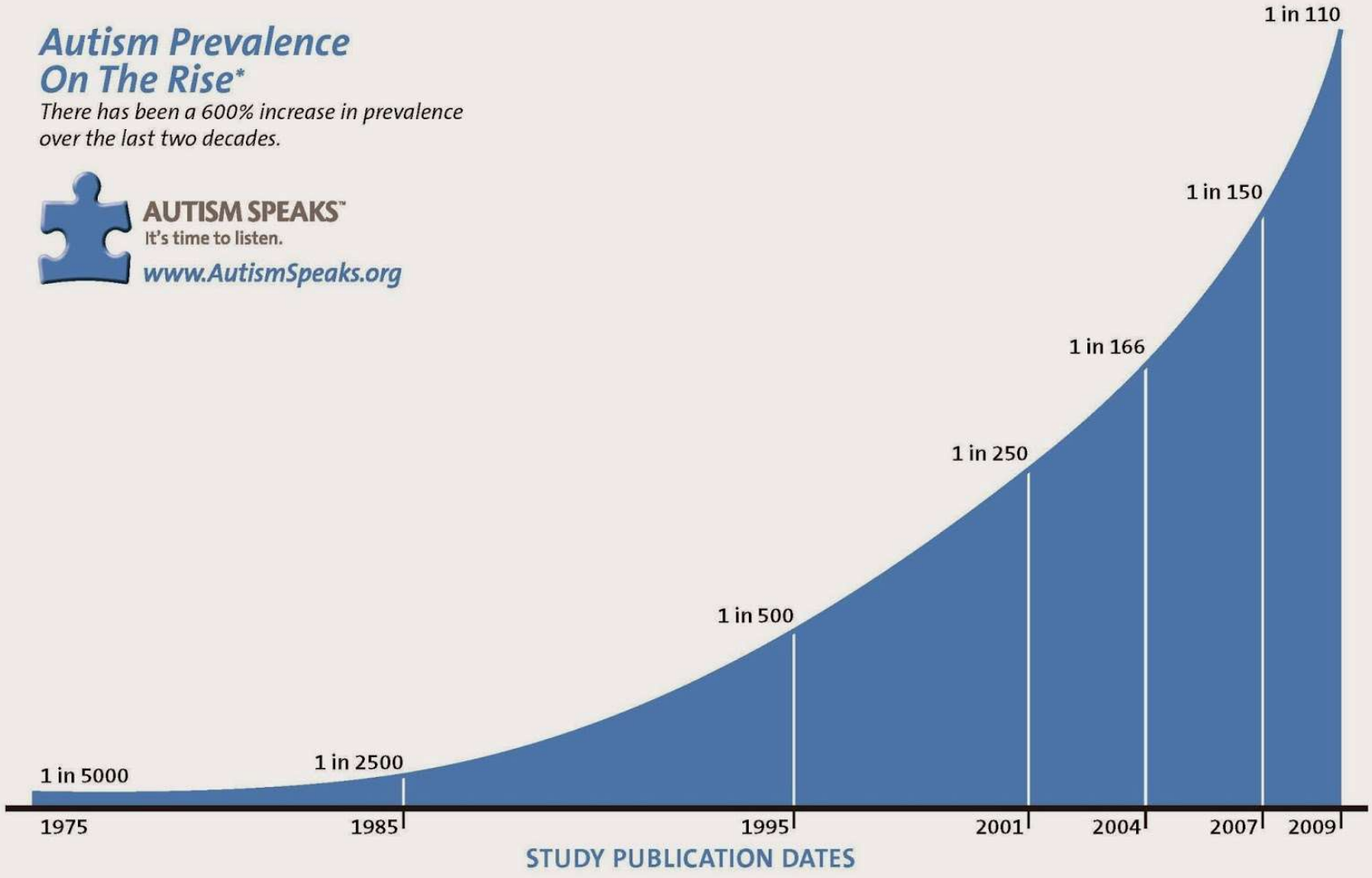

*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.