VACCINE INDUCED IMMUNO-DEFICIENCY

JAMES LYONS-WEILER, PHD

INSTITUTE FOR PURE AND APPLIED KNOWLEDGE

CONCLUSIONS

Whole-population vaccination may be causing immunodeficiency that can be detected at the national level as increased unnecessary infections from vaccine-targeted and non-vaccine targeted pathogens.

Vaccination therefore cannot be expected to “protect” the immunodeficient.

In the long run, whole-population vaccination makes the use of vaccines **a self-defeating prospect** due to vaccine-induced immunodeficiency.

HTTP://IPAKNOWLEDGE.ORG

Retrospective Analyses of Health Outcomes in a Variably Vaccinating Pediatric Practice

Principal Investigator: Paul Thomas, MD

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Using these data, we will study three Specific Aims:

- **Specific Aim 1:** Is vaccination exposure associated with major health outcome categories?

  Patients will be stratified based on vaccine status: "fully vaccinated" per CDC pediatric schedule, partially vaccinated, and unvaccinated. Outcomes to be studied include, but are not limited to:
  - Any neurodevelopmental/neurobehavioral disorder diagnosis (autism spectrum disorder per DSM-5, ADHD, pervasive development disorder, tics, Tourette's syndrome, other);
  - Any allergy or autoimmune disorder (eczema, allergies, asthma, arthritis, IDDM, other) after 18 months of age;
  - Speech-related disorders (apraxia, others)
  - Repetitive motion or movement disorders
  - Social disorders

- **Specific Aim 2**: Within the vaccinated, are there indicators of risk of vaccine-related morbidity/mortality available in early medical reports (<2 years of age)?

  To address this aim, Phased Biomarker Development integrative modeling will be used to study available predictor variables including *family history of autoimmunity, birth weight, older sibling w/adverse events, eczema, vaccine-related fever, vaccine-related febrile seizure, ear infections(otitis media), early exposure to acetaminophen, gestational vaccination (none, single, double)*, and others.

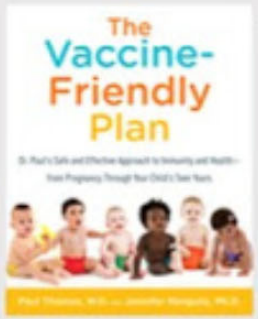
  In addition to outcomes noted in "Specific Aim 1" above, additional outcome variables will include, but are not limited to:

- **Specific Aim 3**: To determine if these models are enhanced by including variables traditionally considered "confounders", such as family history and other variables.

  Here, the same model evaluation will be used but these additional variables will be examined as possible co-predictors of the health effects of vaccination. Our data analysis plan (DAPs) per aim will be published online prior to execution of any analysis. Per national research regulatory standards and requirements, all data will be de-identified by an Honest Broker who will not be involved in the data analysis.

- Inclusion Criteria:
  - Over 3,000 medical records were examined during the quality assurance audit at Dr. Paul Thomas' Integrative Pediatrics practice.

Autism Rates for 3,344 Patients At Integrative Pediatrics



1 in 438

1 in 715

vs.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

1 in 45

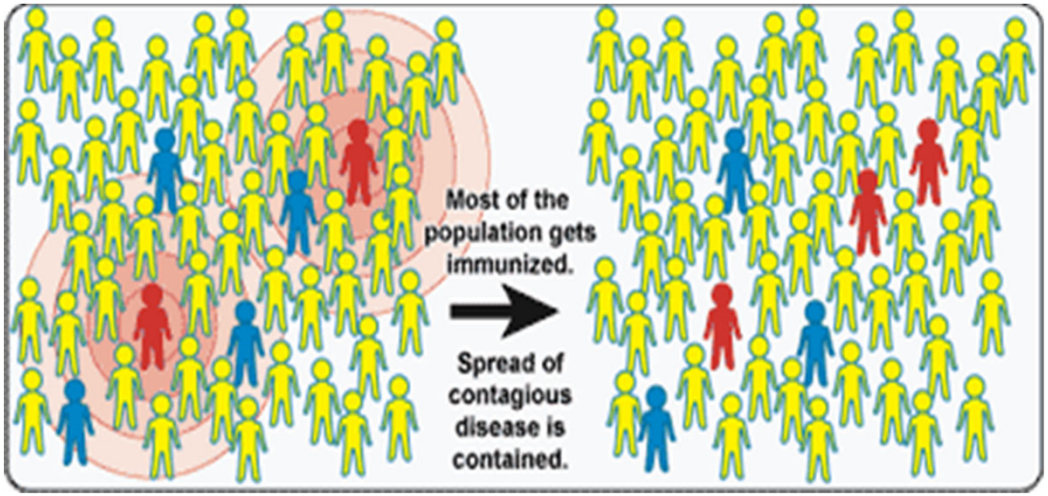
VACCINE EXEMPTION REMOVAL

ONE RATIONALE USED ARGUE FOR

100% VACCINATION IS

“HERD IMMUNITY WILL PROTECT THE “IMMUNODEFICIENT’”

AKA, THE IMMUNOCOMPROMISED



CDC: Vaccination Coverage of Children Remains High

Rates of Unvaccinated, Vaccine-exempt Children Increase Slightly

October 19, 2018 02:13 pm News Staff – A pair of CDC *Morbidity and Mortality Weekly Reports (MMWRs)* released Oct. 12 offered an overview of vaccination status among young children in the United States, most of which was positive.

Vaccination Status of Kindergarteners

The first *MMWR* (www.cdc.gov) focused on vaccine coverage and exemption rates among kindergarteners for the 2017-18 school year and found the median vaccination coverage was 95.1 percent for the state-required dosage series for diphtheria, tetanus and acellular pertussis (DTaP) vaccine.

The report, which summarized vaccine coverage and exemption estimates collected by state and local immunization programs for kindergarteners in 49 states and the District of Columbia, as well as data


Henry Mayo Newhall Hospital.

Caleb Lunetta September 26, 2019 7:53 pm No Comments

40 cases of whooping cough diagnosed last week in Santa Clarita (VIDEO)

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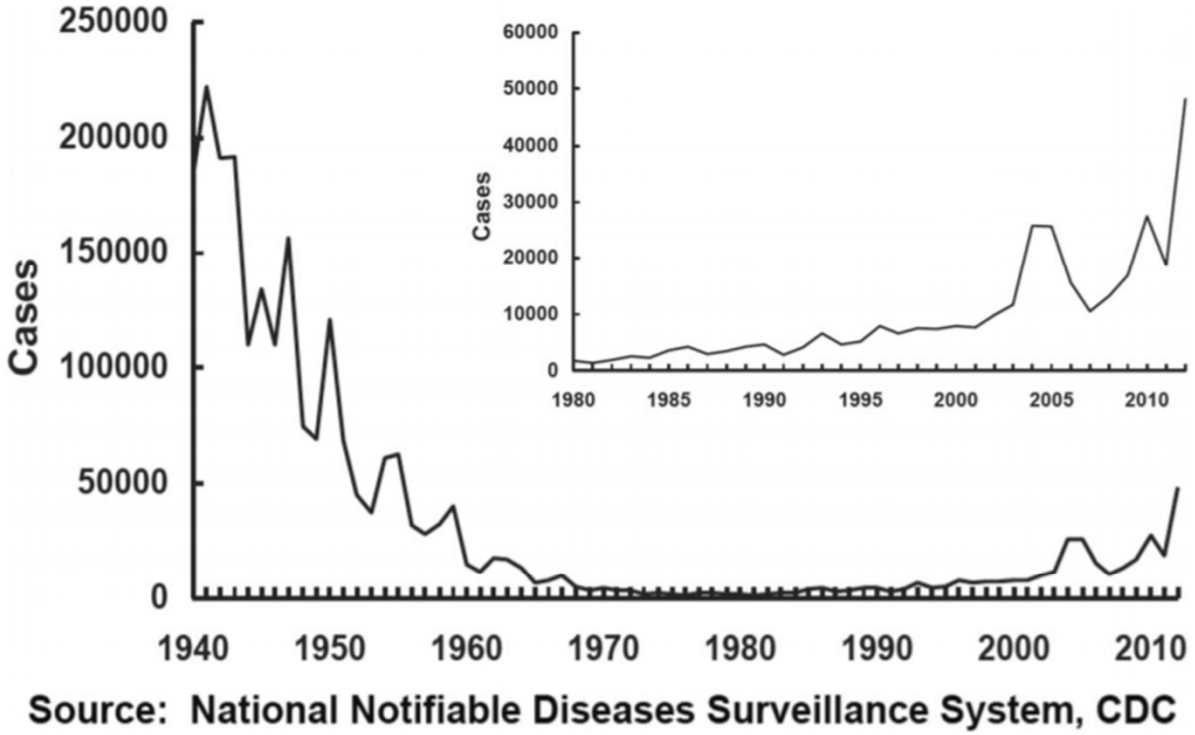
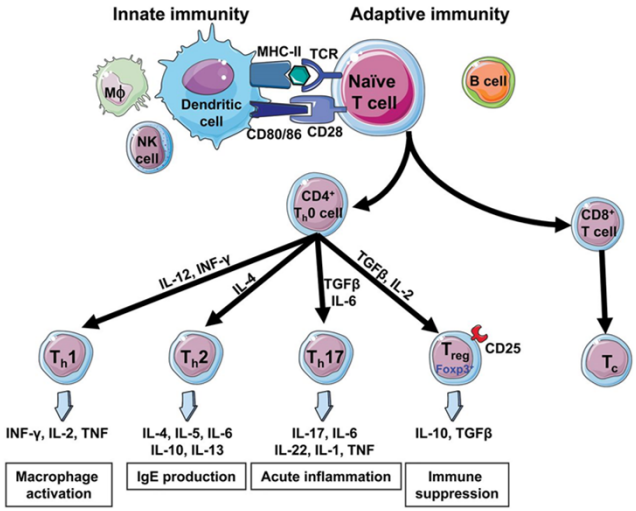


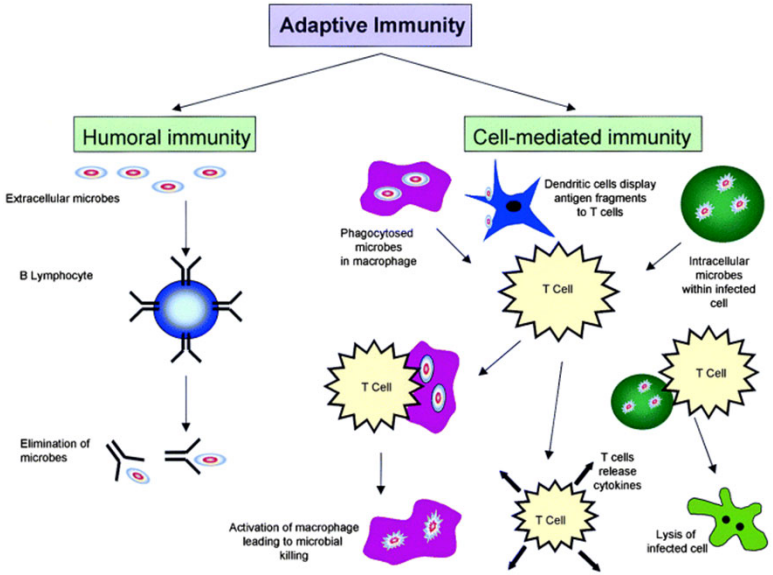
Fig. 1 Pertussis cases in the US, 1940–2012. Data are from the Centers for Disease Control and Prevention via the National Notifiable Diseases Surveillance System

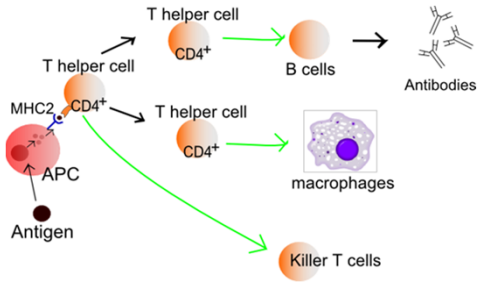
Lapidot and Gill Tropical Diseases, Travel Medicine and Vaccines (2016) 2:26

DEFINITION OF “IMMUNODEFICIENCY”

Immunodeficiency is the state in which an individual has a partially or entirely suppressed adaptive immune system.







HUMAN ADAPTIVE IMMUNE SYSTEM HAS MANY MOVING PARTS!

KNOWN CAUSES OF IMMUNODEFICIENCY

Primary

- Genetics
  - ataxia telangiectasia
  - common variable immunodeficiency
  - severe combined immunodeficiency
  - DiGeorge syndrome
  - Wiskott-Aldrich syndrome
  - X-linked agammaglobulinemia

Secondary

SECONDARY

- HIV INFECTION
- AGE (IMMUNOSENESCENCE)
- CHEMOTHERAPY
- TRANSPLANT IMMUNOSUPPRESSIVE DRUGS
- ANTIBIOTICS
- CHEMICALS
  - *Perfluorooctanoate and Perfluorooctanesulfonate (WAS USED IN SCOTCHGUARD)*
  - *Thimerosal*

EVIDENCE THAT VACCINES MAY INDUCE IMMUNODEFICIENCY

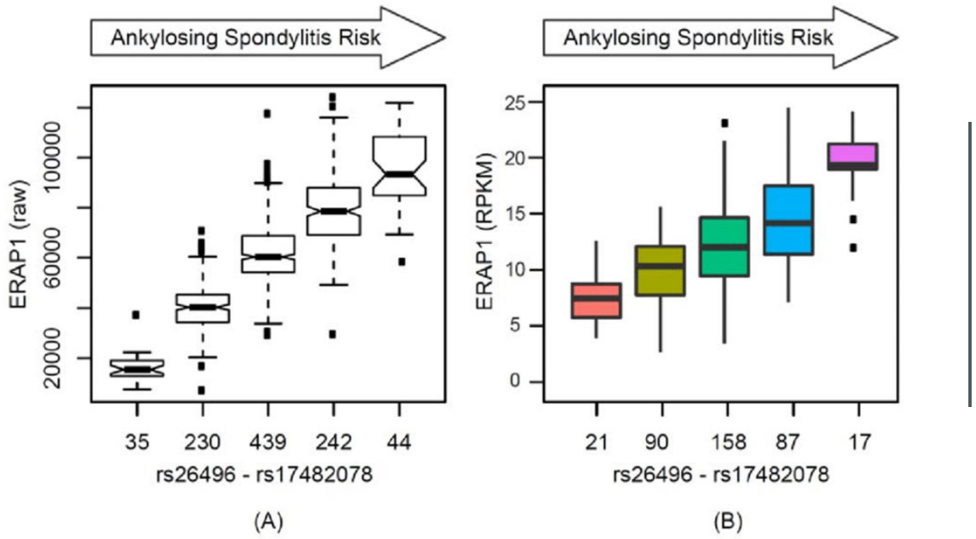
- THIMEROSAL SPECIFICALLY INHIBITS ERAP1
- MITOTOXICITY
- LINKED EPITOPE SUPPRESSION

1. THIMEROSAL

- 50 % ETHYLMERCURY BY WEIGHT
- ANTI-FUNGAL ADDITIVE USED IN MULTI-DOSE VIALS
- ABOUT 80% OF INFLUENZA VACCINES IN THE US MARKET CONTAIN THIMEROSAL
- >250 MCG PER DOSE

THIMEROSAL &
ENDOPLASMIC RETICULUM AMINOPEPTIDASE 1 (ERAP1)

- ERAP1 shortens proteins *en route* to be presented on the surface of MHC Class 1 cells



nature COMMUNICATIONS

ARTICLE

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DOI: 10.1038/ncomms14357 OPEN

Connecting genetic risk to disease end points through the human blood plasma proteome

Karsten Suhre[1,*], Matthias Arnold[2,*], Aditya Mukund Bhagwat[3,*], Richard J. Cotton[3,*], Rudolf Engelke[3,*], Johannes Raffler[2,*], Hina Sarwath[3,*], Gaurav Thareja[1,*], Annika Wahl[4,5,*], Robert Kirk DeLisle[6], Larry Gold[6], Marija Pezer[7], Gordan Lauc[7], Mohammed A. El-Din Selim[8], Dennis O. Mook-Kanamori[9], Eman K. Al-Dous[10], Yasmin A. Mohamoud[10], Joel Malek[10], Konstantin Strauch[11,12], Harald Grallert[4,5,13], Annette Peters[5,13,14], Gabi Kastenmüller[2,13], Christian Gieger[4,5,13,**] & Johannes Graumann[3,**,†]

Genome-wide association studies (GWAS) with intermediate phenotypes, like changes in metabolite and protein levels, provide functional evidence to map disease associations and translate them into clinical applications. However, although hundreds of genetic variants have been associated with complex disorders, the underlying molecular pathways often remain elusive. Associations with intermediate traits are key in establishing functional links between GWAS-identified risk-variants and disease end points. Here we describe a GWAS using a highly multiplexed aptamer-based affinity proteomics platform. We quantify 539 associations between protein levels and gene variants (pQTLs) in a German cohort and replicate over half of them in an Arab and Asian cohort. Fifty-five of the replicated pQTLs are located *in trans*. Our associations overlap with 57 genetic risk loci for 42 unique disease end points. We integrate this information into a genome-proteome network and provide an interactive web-tool for interrogations. Our results provide a basis for novel approaches to pharmaceutical and diagnostic applications.

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NATURE COMMUNICATIONS | 8:14357 | DOI: 10.1038/ncomms14357 | www.nature.com/naturecommunications 1

GENETIC VARIANTS IN ERAP1 AND ERAP1 ACTIVITY CONFER AUTOIMMUNE RISK

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 Str[illegible]*[,†]

[†]National Center for

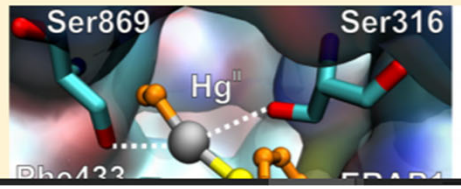
[§]Institut National de

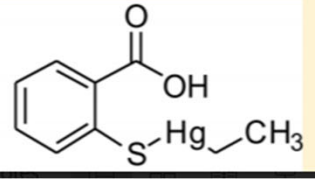
National de la Reche

“Cell-based analysis indicated that thimerosal can effectively reduce ERAP1- dependent cross-presentation by dendritic cells in a dose-dependent manner.”

Supporting Infor

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





THIMEROSAL-CONTAINING FLU VACCINES

- INCREASED THE RISK OF NON-INFLUENZA RESPIRATORY VIRUS INFECTIONS BY

  390/88 = 4.43 (p<0.01)

BRIEF REPORT

Increased Risk of Noninfluenza Respiratory Virus Infections Associated With Receipt of Inactivated Influenza Vaccine

Benjamin J. Cowling,[1] Vicky J. Fang,[1] Hiroshi Nishiura,[1,2] Kwok-Hung Chan,[3] Sophia Ng,[1] Dennis K. M. Ip,[1] Susan S. Chiu,[4] Gabriel M. Leung,[1] and J. S. Malik Peiris[1,5]

[1]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China; [2]PRESTO, Japan Science and Technology Agency, Saitama; [3]Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, [4]Department of Pediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, and [5]Centre for Influenza Research, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had an increased risk of virologically-

METHODS

Recruitment and Follow-up of Participants

In a double-blind randomized controlled trial, we randomly allocated children aged 6–15 years to receive 2008–2009 seasonal trivalent influenza inactivated vaccine (TIV; 0.5 mL Vaxigrip; Sanofi Pasteur) or placebo [16]. Serum specimens were obtained from participants before vaccination from November through December 2008, a month after vaccination, in midstudy around April 2009, and at the end of the study from August through October 2009. Participants were followed up for illnesses through symptom diaries and telephone calls, and illness reports in any household member triggered home visits during which nasal and throat swab specimens (NTSs) were collected from all household members. We defined the follow-up period for each participant from 14 days after receipt of TIV or placebo to collection of midstudy serum samples as the winter season and from collection of midstudy samples through final serum sample obtainment as the summer season.

COWLING ET AL:

- **Examined the efficacy of TCV's on influenza and effect on other non-influenze RV infection**
- **DID NOT** FIND A STATISTICALLY SIGNIFICANT REDUCTION OF INFLUENZA INFECTION FOLLOWING TCV
- **DID** FIND A SIGNIFICANT INCREASED RISK OF

Non-influenza respiratory virus infection among TCV recipients:

-rhinovirus infection

-coxsackie/echovirus infection

Financial support. This work was supported by the Area of Excellence Scheme of the Hong Kong University Grants Committee (grant number AoE/M-12/06), the Hong Kong University Research Council Strategic Research Theme of Public Health, the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant number U54 GM088558), and the Research Fund for the Control of Infectious Disease, Food and Health Bureau, Government of the Hong Kong SAR (grant number PHE-2). The funding bodies had no role in study design, data collection and analysis, preparation of the manuscript, or the decision to publish.

Potential conflicts of interest. B. J. C. has received research funding from MedImmune. D. K. M. I. has received research funding from Roche. J. S. M. P. receives research funding from Crucell MV. All other authors report no potential conflicts.

spective: application
results. J Am Statist
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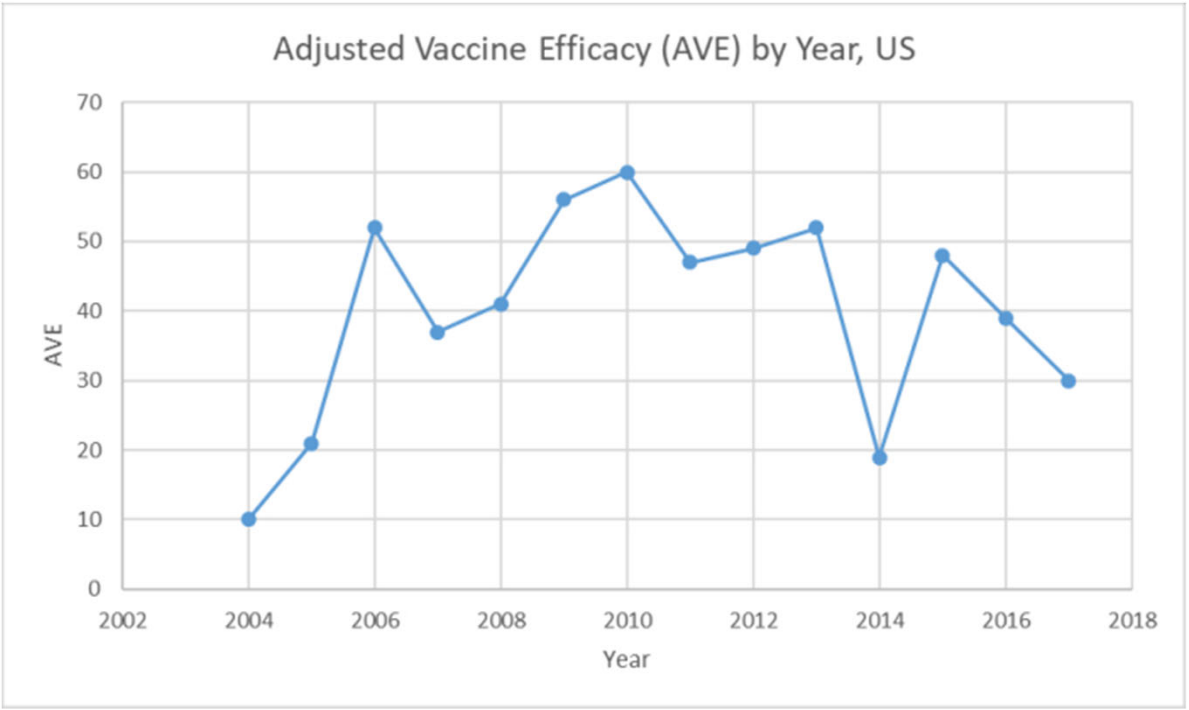
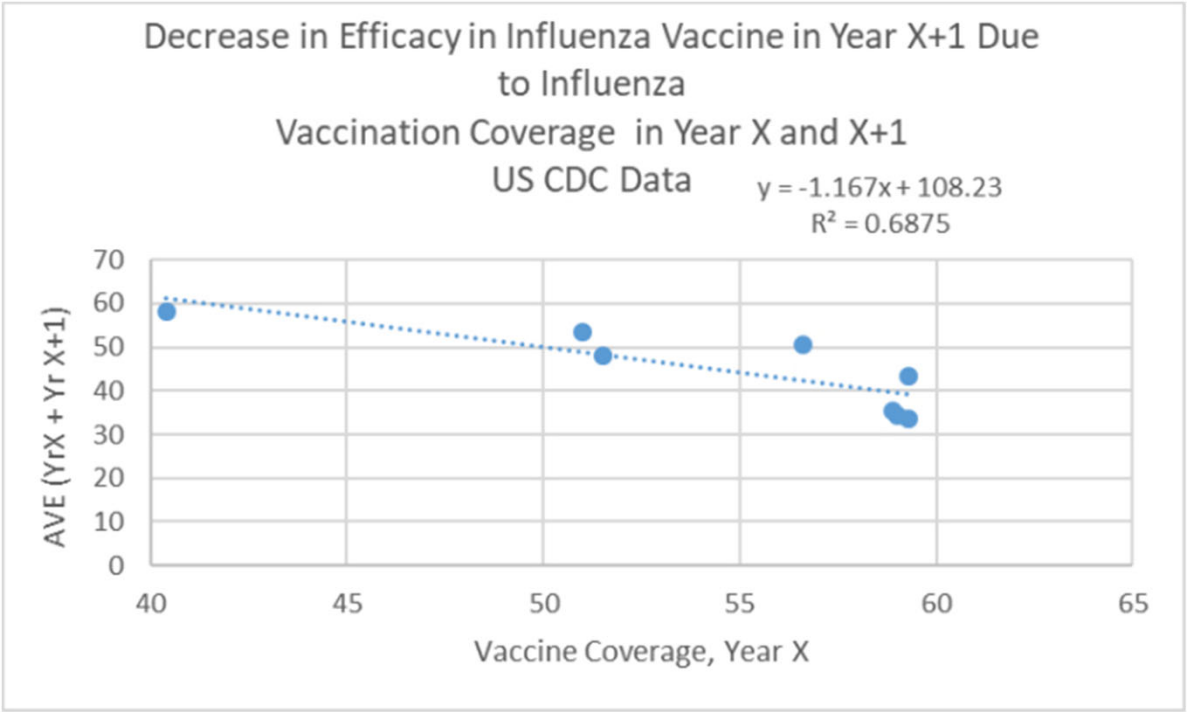
INFLUENZA VACCINE RECORD

- USA
- 2004-201S7



INFLUENZA VACCINE UPTAKE DECREASES EFFICACY OF FLU VACCINE… ???

- JLW RESULT
- IPAK
- THIMEROSAL?
  NON-INFLUENZA "FLU"?
- "FLU-SYNDROME"



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

"Overall our findings suggest that Al induces ER stress and ROS generation which compromises the antioxidant defenses of neuronal cells thereby promoting neuronal apoptosis in p53 independent pathway."

Abstract

Aluminium (Al) is house hold utensils, me ns in a variety of neurod e of Al in endoplasmic r ne. 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 inhibitors of specific and pan-caspases, we observed significant protection against neuronal cell death upon inhibition of

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Lyons-Weiler, Autism Open Access 2018, 8:1
DOI: 10.4172/2165-7890.1000224

Review Article Open Access

Autism is an Acquired Cellular Detoxification Deficiency Syndrome with Heterogeneous Genetic Predisposition

James Lyons-Weiler*

Institute for Pure and Applied Knowledge, USA

Abstract

Neurodevelopmental disorders, including autism spectrum disorders, have a complex biological and r
diverse genetic risk and myriad environmental exposures. Teasing apart the role of specific stressors is
to the large number of apparently contributing associations, gene x environment interactions and phen
these conditions have been rare, making causality assessment at the population level infeasible. Only a fe
tested for association with autism, and it has been shown that improved diagnosis only explains a percen
diagnosis. Now the rates are so high in some countries that public school programs cannot handle to large numbers of special
needs students, and professionals are quitting their jobs due to security concerns. Here, I present a mechanistic biomedical
process model (theory) of the pathophysiology of autism that reconciles the apparent paradox between the high degree of causal

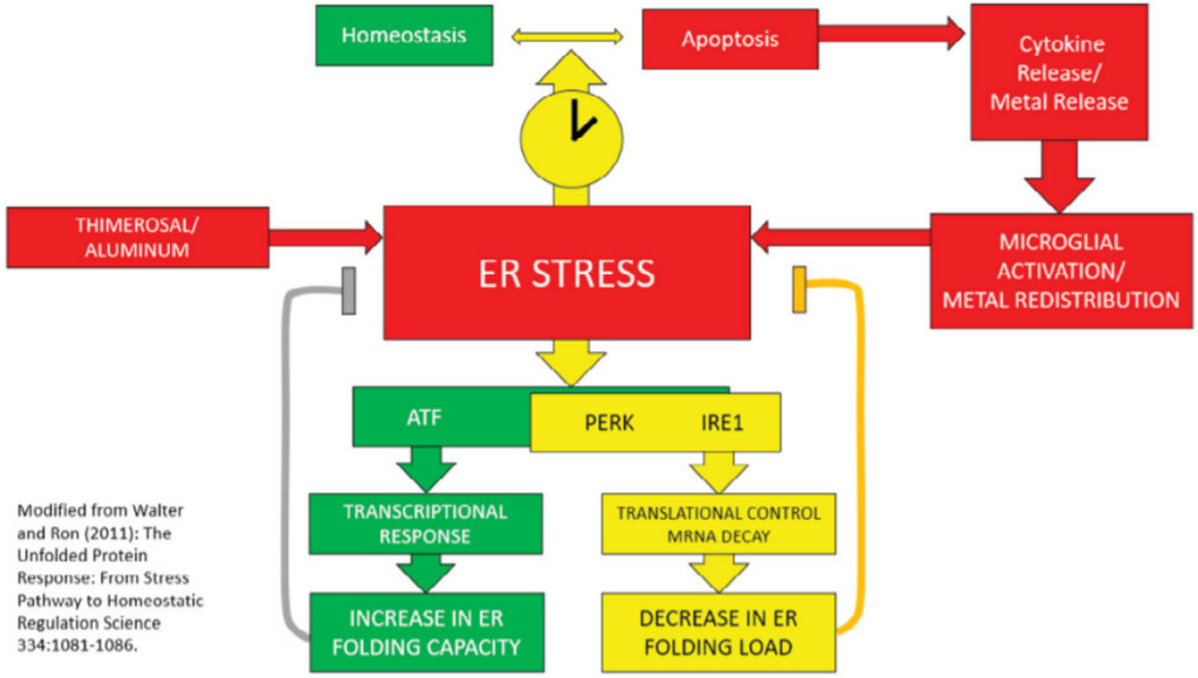

Figure 1: The canonical ER stress response pathway is activated in new cells due to the apoptotic release and redistribution of metals (and other toxins), spreading the ER response and initiating chronic microglial activation. With astrocytic dysfunction, the excess glutamate contributes to chronic gliosis, which is both a consequence and contributor to aberrant pruning during

ER stress include direc
generation, and ER cal
found that aluminum
[112]. Stamogiannos fo
protein ERAP1, which,
generation of most HL
ERAP1 is essential to tr
required for presentatic
found that annual vacci
CD8+ T cell immunity
which includes thimero

In neurodegenerati

Journal of Trace Elements in Medicine and Biology 48 (2018) 67–73

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

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ARTICLE INFO

Keywords:
Aluminum
Minimum risk level
Provisional tolerable weekly intake
Regulatory elements
Pediatric dosing
No observed adverse effect level
Vaccines

ABSTRACT

FDA regulations require safety testing of constituent ingredients in drugs (21 CFR 610.15). With the exception of extraneous proteins, no component safety testing is required for vaccines or vaccine schedules. The dosing of aluminum in vaccines is based on the production of antibody titers, not safety science. Here we estimate a Pediatric Dose Limit that considers body weight. We identify several serious historical missteps in past analyses of provisional safe levels of aluminum in vaccines, and provide updates relevant to infant aluminum exposure in the pediatric schedule considering pediatric body weight. When aluminum doses are estimated from Federal Regulatory Code given body weight, exposure from the current vaccine schedule are found to exceed our esti-

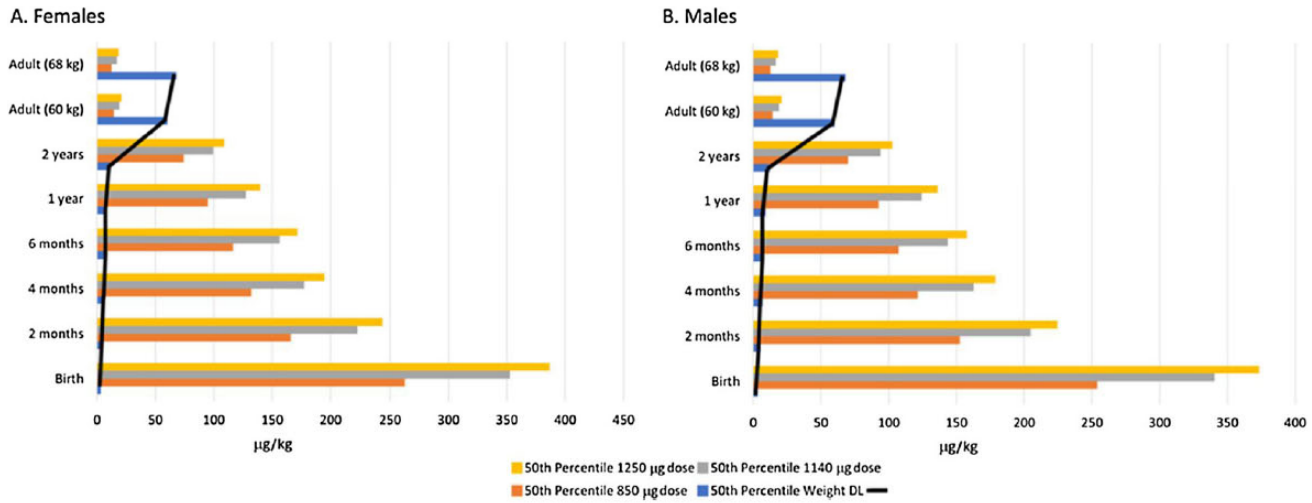


Fig. 2. FDA Doses and exposures adjusted by body weight: Comparison between Infants and an Adult.
In a male child from birth through 36 months at the 50th percentile body weight, the FDA dose of 850 μg adjusted by body weight demonstrates that an adult weighing 60 kg rece significantly less aluminum per injection per kg compared to a child, particularly those children with lower body weights.

Table 1
FDA Dose Adjusted by Body Weight (μg/kg), Birth through Adulthood, US Population.

JECFA provisional tolerable daily intake from dietary and additive exposures of 140 μg/kg/day and current provisional tolerable daily

When adjusted to body weight (μg/kg) and compared to a 60–68 kg adult, the aluminum load is significantly higher in the birth through 24-month age cohort.

The scheduled pediatric vaccinations in 2016 have significantly particularly the use of TDaP, has changed. The combined doses of aluminum at 2, 4, and 6 months are 1225 μg, 975 μg, and 1225 μg respectively (Table 2), and are not determined considering infant and

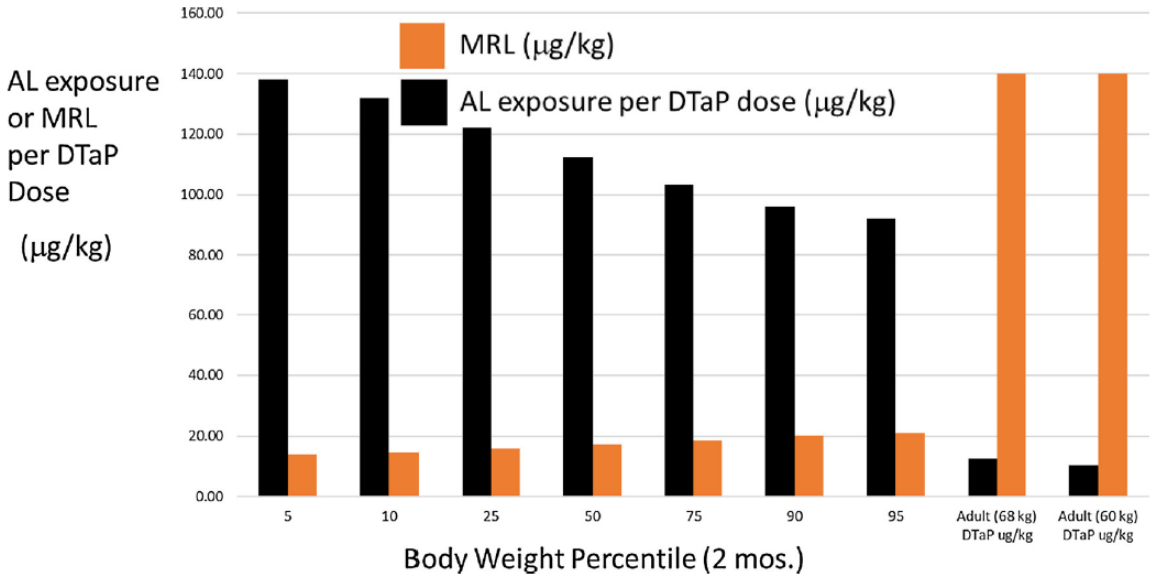
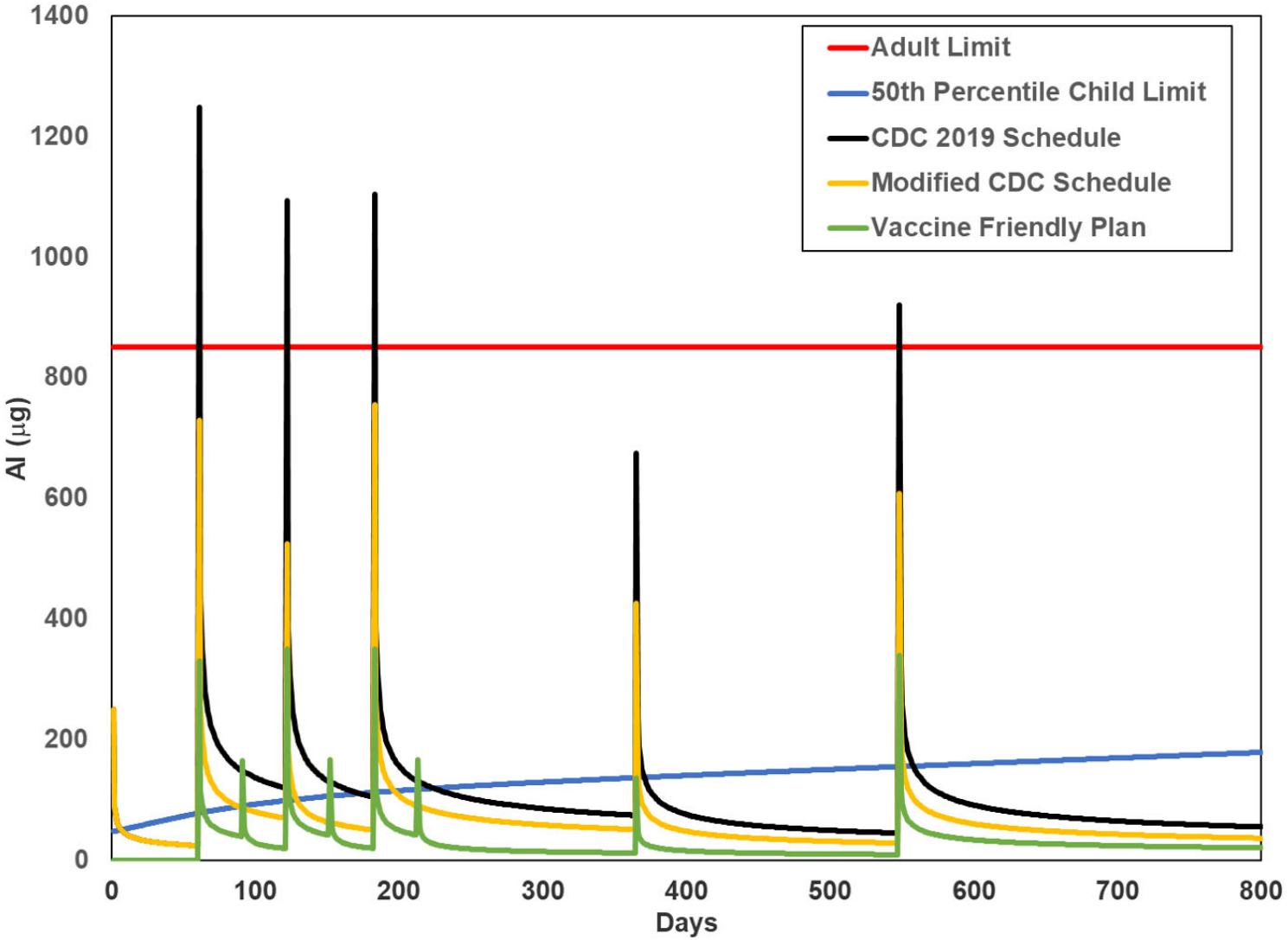
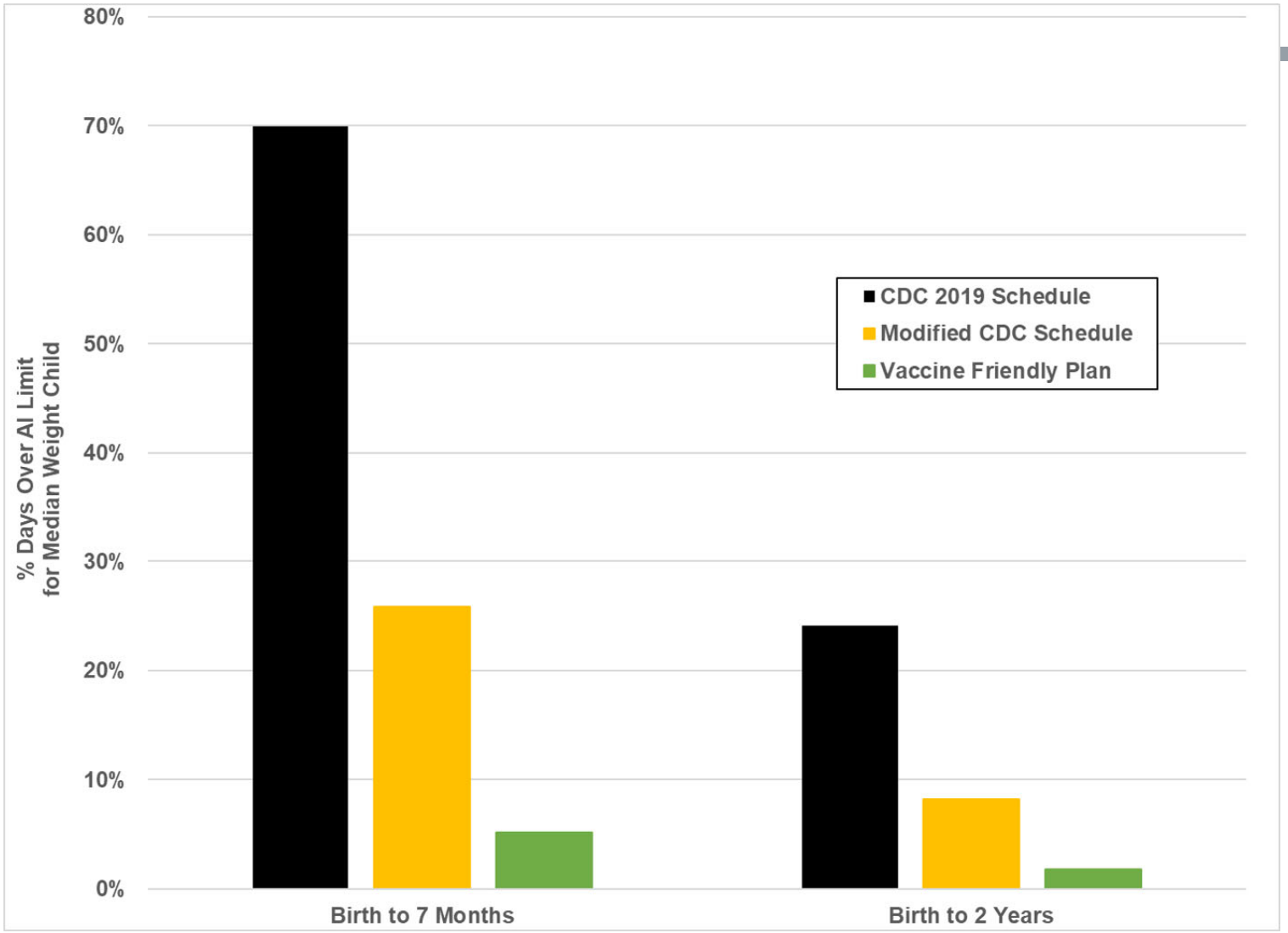


Fig. 4. Comparison of the Calculated Pediatric MRL and the AL Exposures from DTaP Vaccine for Children (and Adults) using Clark's Rule to Accommodate Pediatric Body Weights kg, per day, at 2 months and for Adult).



IN REVIEW

The Institute for Pure and Applied Knowledge
IPAK
Reducing Human Pain and Suffering Through Knowledge



IN REVIEW

The Institute for Pure and Applied Knowledge
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Reducing Human Pain and Suffering Through Knowledge

MITOTOXICITY

- THIMEROSAL (PRESERVATIVE)
- ALUMINUM (ADJUVANTS)
- AUTOIMMUNE MITOCHONDRIAL DEFICIENCY

Hindawi Publishing Corporation
Journal of Toxicology
Volume 2012, Article ID 373678, 12 pages
doi:10.1155/2012/373678

Research Article

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

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THIMEROSAL-INDUCED MITOTOXICITY

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http://dx.doi.org/10.1155/2013/801517

Research Article

B-Lymphocytes from a Population of Children with Autism Spectrum Disorder and Their Unaffected Siblings Exhibit Hypersensitivity to Thimerosal

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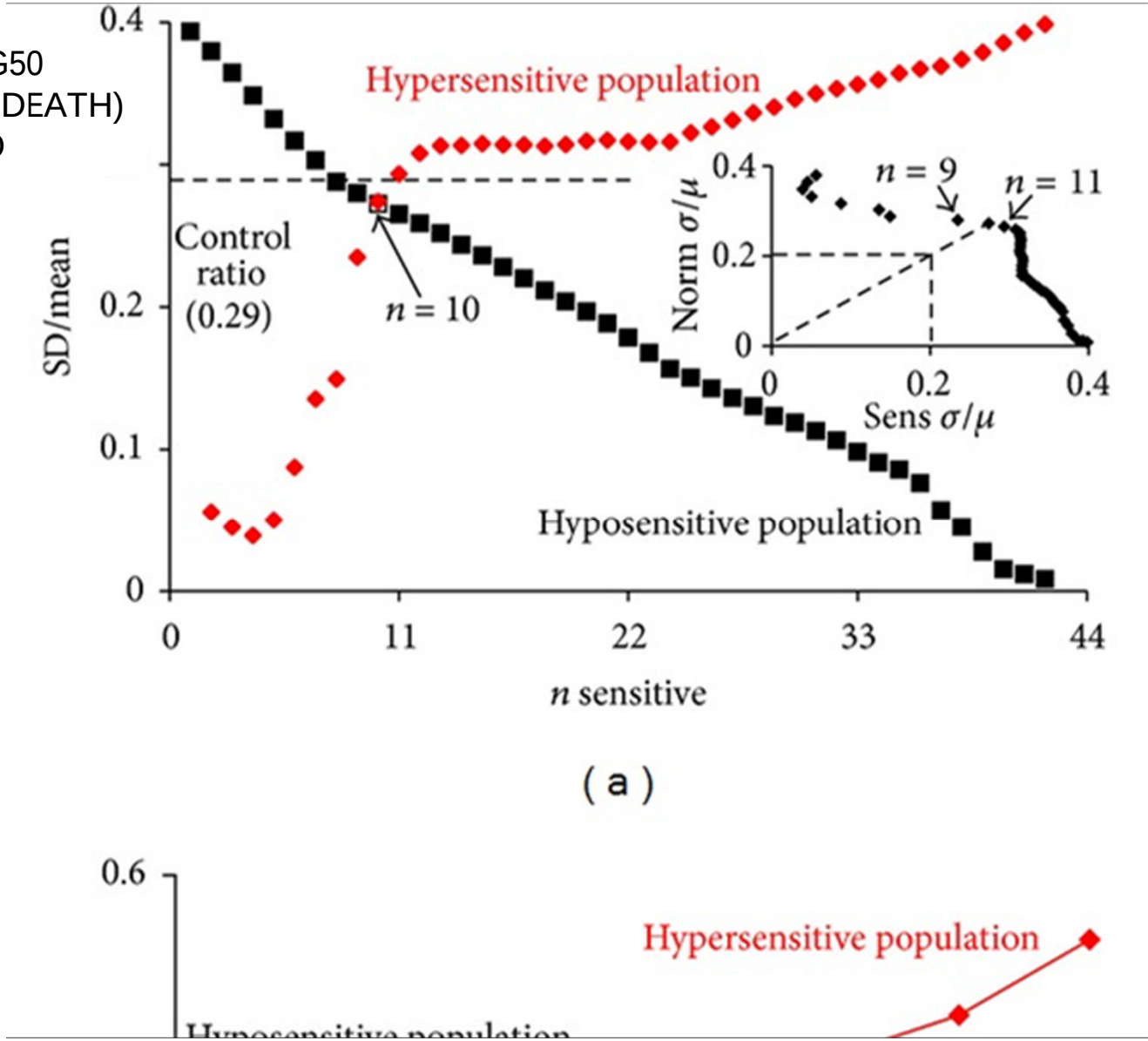
SHARPE ET AL. 2013

- B- Lymphocytes exposed to thimerosal
- 11 families
- ASD + Sibs
- Control (No ASD)

LDH-G50 (CELL DEATH) RATIO



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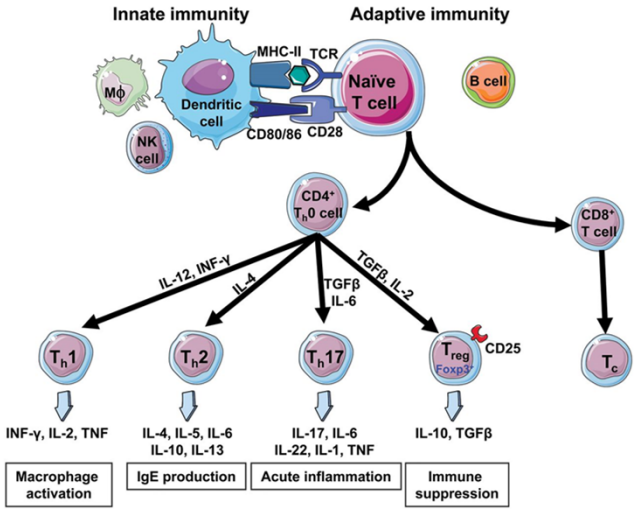

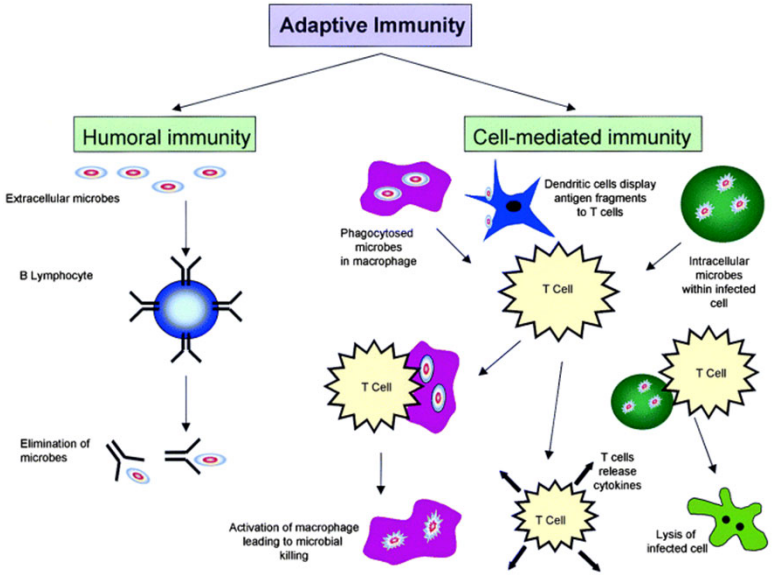

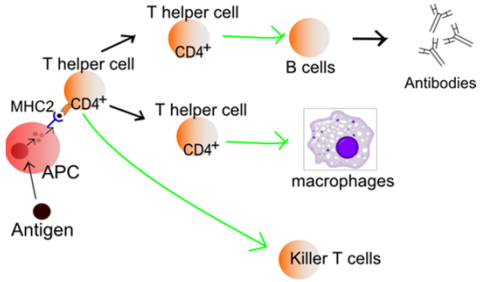

- COMBINED WITH GENETIC MITOCHONDRIAL IMPAIRMENT…

ALUMINUM

Journal of Neuroscience Research 87:1474–1483 (2009)

Aluminum-induced Defective Mitochondrial Metabolism Perturbs Cytoskeletal Dynamics in Human Astrocytoma Cells

J. Lemire,[1] R. Mailloux,[1] S. Puiseux-Dao,[2] and V. D. Appanna[1]*

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Although aluminum (Al), a known environmental toxin, has been implicated in a variety of neurological disorders, the molecular mechanism responsible for these conditions is not fully understood. In this report, we demonstrate the ability of Al to trigger mitochondrial dysfunction and ineffective adenosine triphosphate (ATP) production. This situation severely affected cytoskeletal dynamics. Whereas the control cells had well-defined structures, the Al-exposed astrocytoma cells appeared as globular structures. Creatine kinase (CK)

gradient, which is tapped to drive ATP formation (Yoshida et al., 2001). Complex eukaryotes also rely on other sources of ATP such as phosphogens in order to sustain energy demands (Sauer and Schlattner, 2004). Highly oxidative tissues such as the human brain and skeletal muscle invoke creatine kinase (CK) to produce ATP from phosphocreatine when energy is in high demand (Saks et al., 1996).

The brain consumes the most energy in the human body. Indeed, neurons rely on a steady supply of ATP

LEMIRE ET AL. ALUMINUM IMPAIRS CELLULAR ENERGETICS AND CYTOSKELETAL STRUCTURE

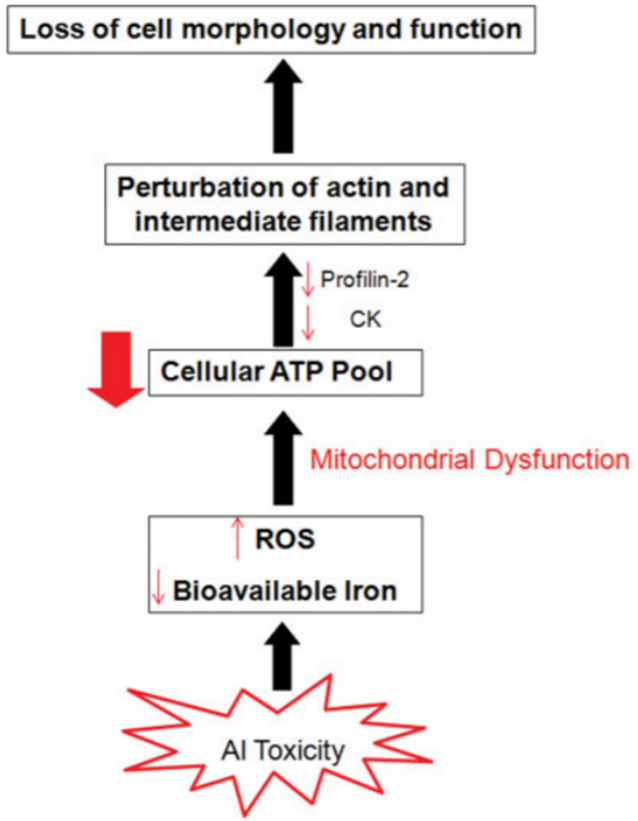
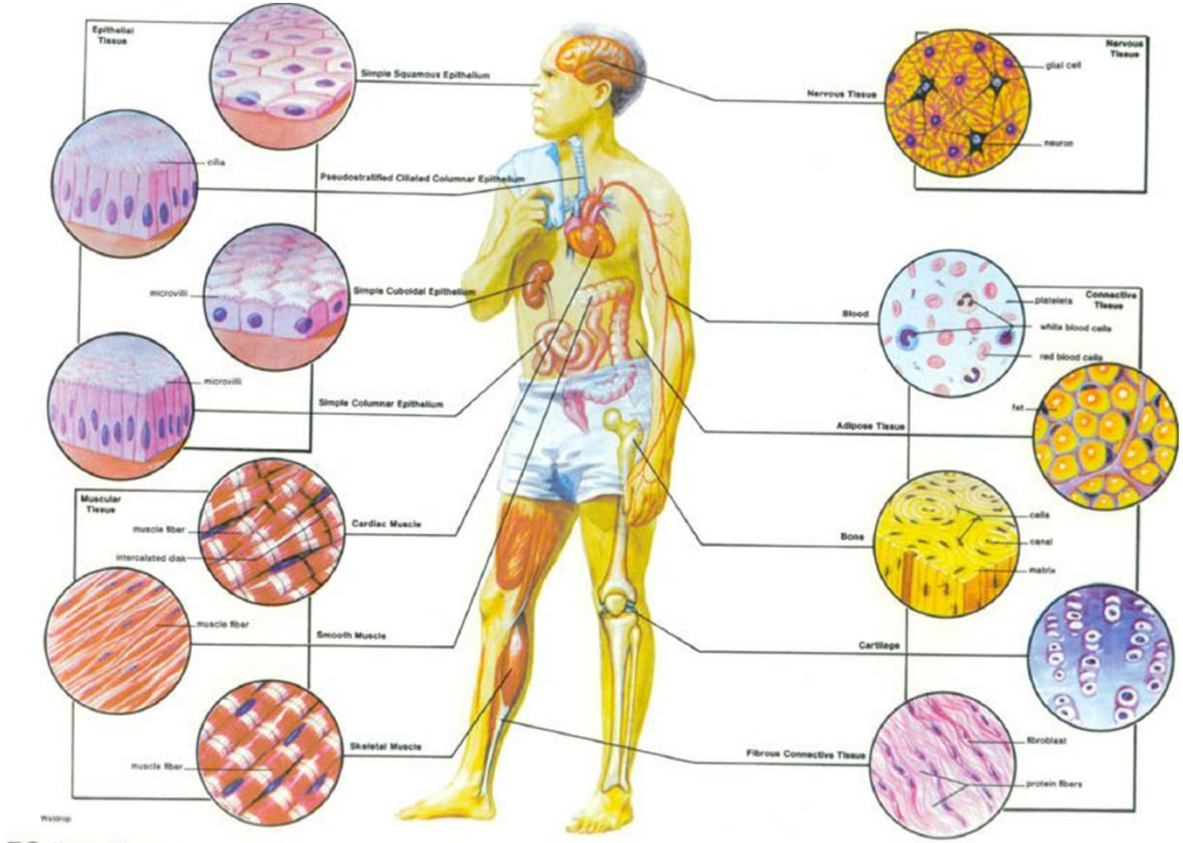
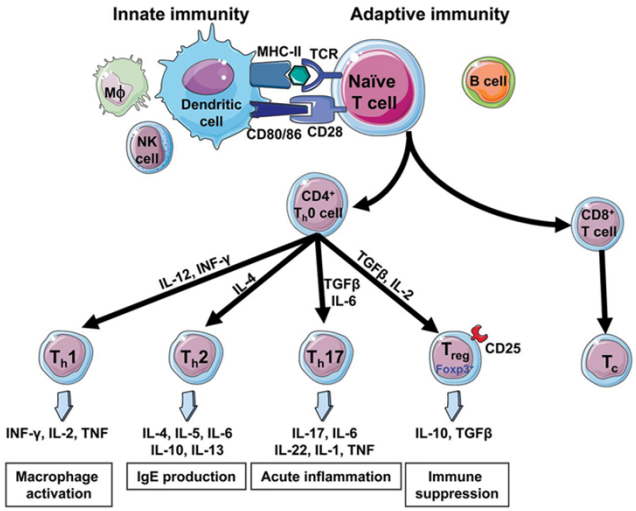


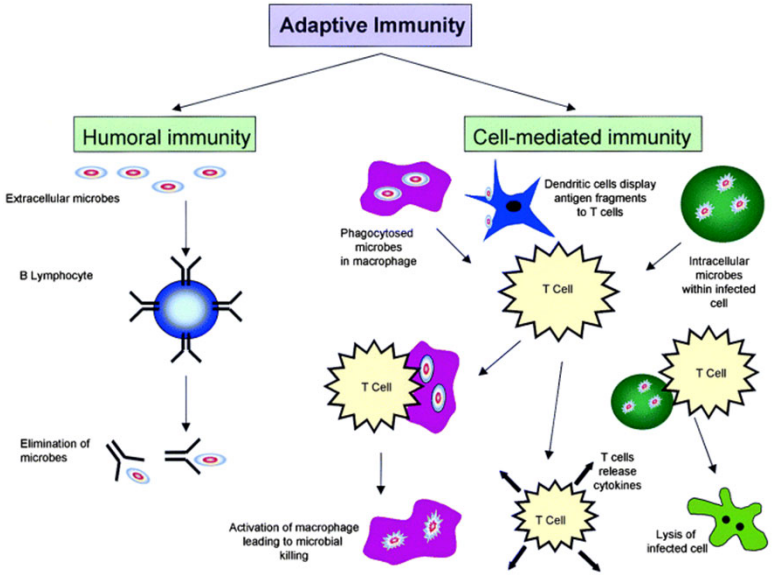
Fig. 9. Molecular link between Al toxicity and morphological perturbation in human astrocytoma cells. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

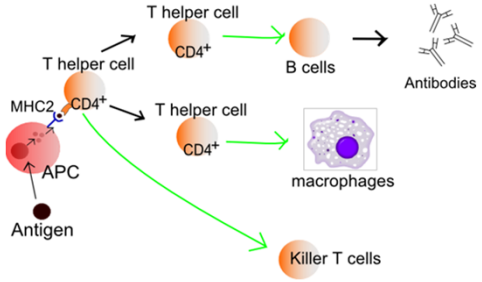
ALUMINUM



59 Human Tissues
Figure 9.1







- COMBINED WITH THIMEROSAL AND GENETIC MITOCHONDRIAL IMPAIRMENT…

Lyons-Weiler and Ricketson, 2018

- How did the FDA determine that 850 ug of aluminum is safe for an adult?
- Has the FDA published a minimum safe level (MSL) of aluminum doses in vaccines for children?
- If not, can we estimate a MSL at a given body weight expressed as ug/kg/day?

FDA (Mitkus et al.) Claimed Aluminum in Vaccines is Safe

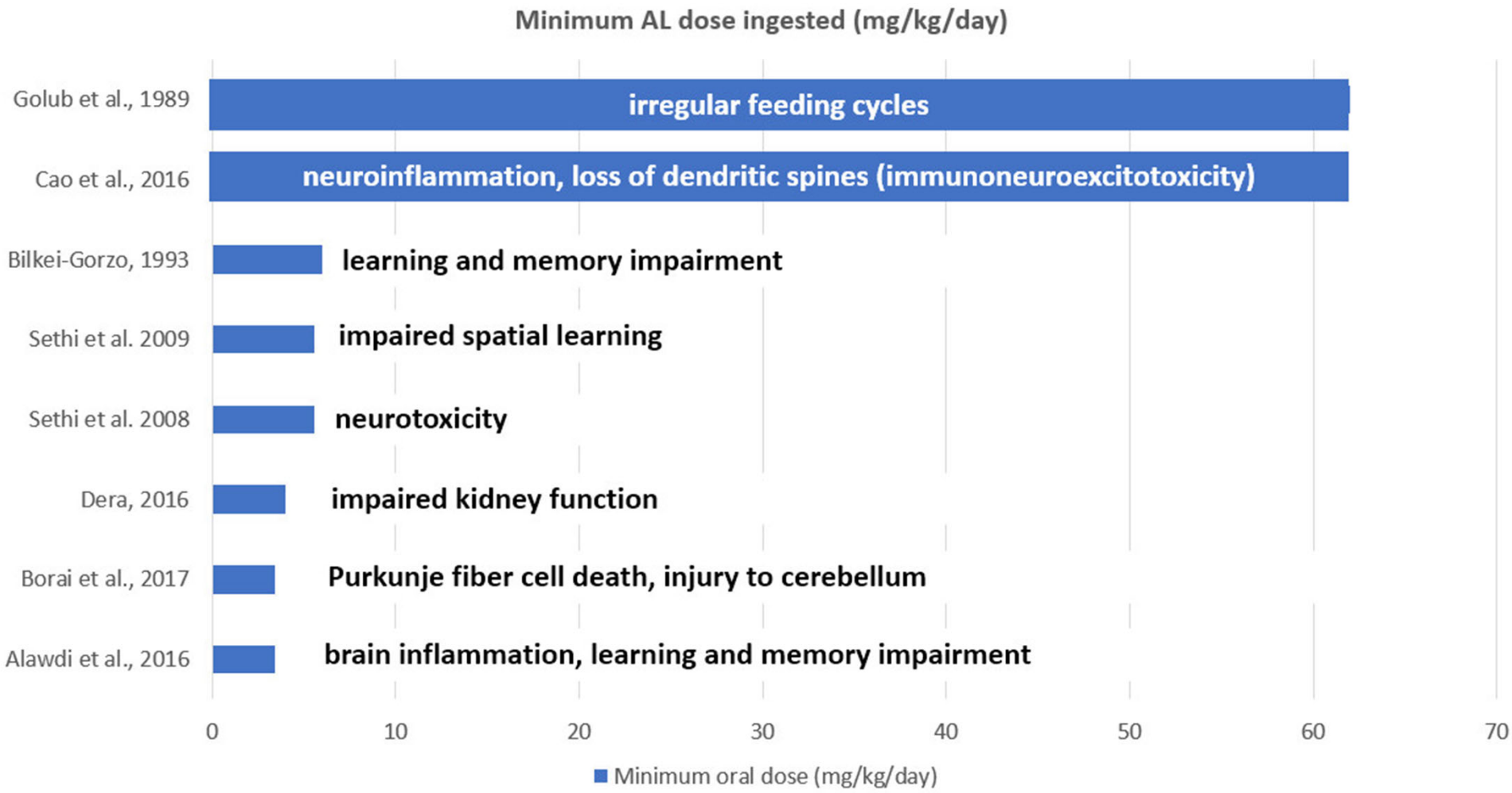
Their analysis (model-only) used estimates from:

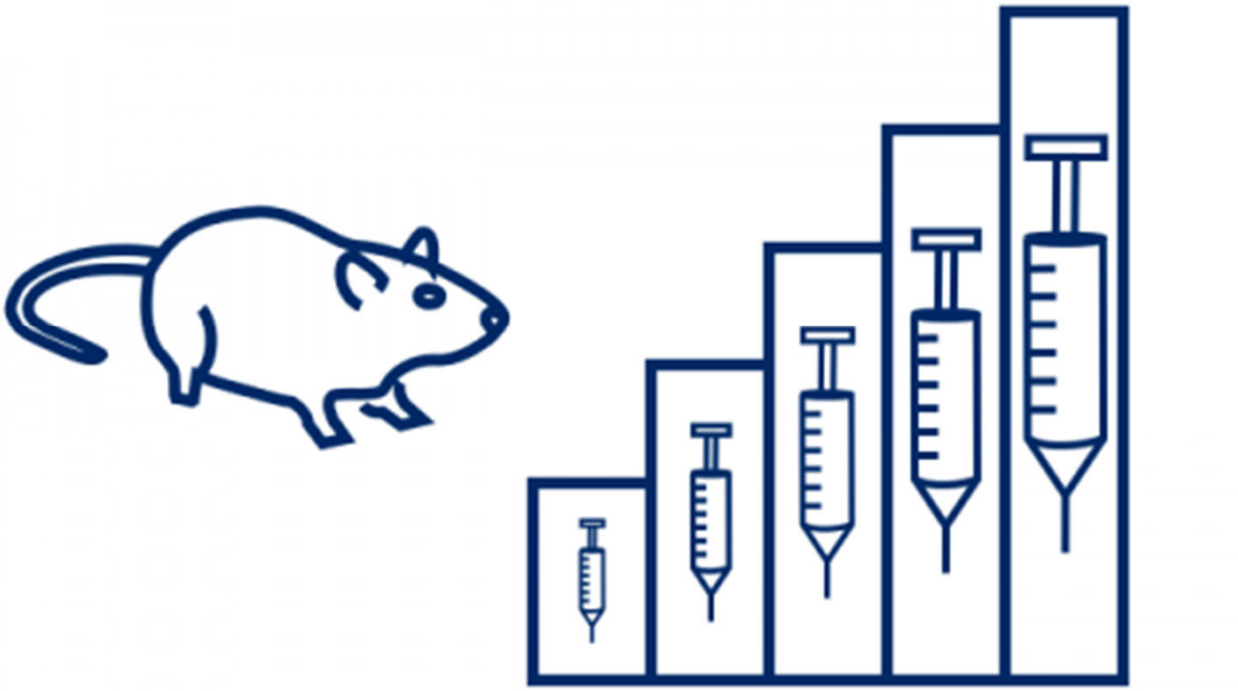
ORAL forms of aluminum, not **INJECTED**

ADULT mice, not **INFANT** mice

MICE, not **HUMAN** studies

Expressed safe levels per dose independent of body weight or time, **not ug/kg/day**


Minimum AL dose ingested (mg/kg/day)
Golub et al., 1989
irregular feeding cycles
Cao et al., 2016
neuroinflammation, loss of dendritic spines (immunoneuroexcitotoxicity)
Bilkei-Gorzo, 1993
learning and memory impairment
Sethi et al. 2009
impaired spatial learning
Sethi et al. 2008
neurotoxicity
Dera, 2016
impaired kidney function
Borai et al., 2017
Purkunje fiber cell death, injury to cerebellum
Alawdi et al., 2016
brain inflammation, learning and memory impairment
0
10
20
30
40
50
60
70
Minimum oral dose (mg/kg/day)



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Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

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ARTICLE INFO

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Minimum risk level
Provisional tolerable weekly intake
Regulatory elements
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No observed adverse effect level
Vaccines
Neonatal vaccination
Neurotoxins

ABSTRACT

FDA regulations require safety testing of constituent ingredients in drugs (21 CFR 610.15). With the exception of extraneous proteins, no component safety testing is required for vaccines or vaccine schedules. The dosing of aluminum in vaccines is based on the production of antibody titers, not safety science. Here we estimate a Pediatric Dose Limit that considers body weight. We identify several serious historical missteps in past analyses of provisional safe levels of aluminum in vaccines, and provide updates relevant to infant aluminum exposure in the pediatric schedule considering pediatric body weight. When aluminum doses are estimated from Federal Regulatory Code given body weight, exposure from the current vaccine schedule are found to exceed our estimate of a weight-corrected Pediatric Dose Limit. Our calculations show that the levels of aluminum suggested by the currently used limits place infants at risk of acute, repeated, and possibly chronic exposures of toxic levels of aluminum in modern vaccine schedules. Individual adult exposures are on par with Provisional Tolerable Weekly Intake "limits", but some individuals may be aluminum intolerant due to genetics or previous exposures. Vaccination in neonates and low birth-weight infants must be re-assessed; other implications for the use of aluminum-containing vaccines, and additional limitations in our understanding of neurotoxicity and safety levels of aluminum in biologics are discussed.

LINKED EPITOPE SUPPRESSION

- The immune response to an antigen is driven by the context in which it was first encountered
- Tolerance induced to a single T cell epitope inhibits the response to all epitopes in the same protein.
- Preferential responses of memory B cells following secondary exposure to vaccine components
- Memory B cells outcompete naive B cells for access to Bordetella epitopes

Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

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Division of Bacterial, Parasitic and Allergenic Products, Center for Biologics Evaluation and Research, US Food and Drug Administration, Bethesda, MD, 20892

Edited by Rino Rappuoli, Novartis Vaccines and Diagnostics Srl, Siena, Italy, and approved October 22, 2013 (received for review August 5, 2013)

Pertussis is a highly contagious respiratory illness caused by the bacterial pathogen *Bordetella pertussis*. Pertussis rates in the United States have been rising and reached a 50-y high of 42,000 cases in 2012. Although pertussis resurgence is not completely understood, we hypothesize that current acellular pertussis (aP) vaccines fail to prevent colonization and transmission. To test our hypothesis, infant baboons were vaccinated at 2, 4, and 6 mo of age with aP or whole-cell pertussis (wP) vaccines and challenged with *B. pertussis* at 7 mo. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring leukocytosis and symptoms. Baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonization, did not clear the infection faster than naïve animals, and readily transmitted *B. pertussis* to unvaccinated contacts. Vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals. By comparison, previously infected animals were not colonized upon secondary infection. Although all vaccinated and previously infected animals had robust serum antibody responses, we found key differences in T-cell immunity. Pre-

therapeutic for established disease, and the highly contagious nature of pertussis. Although a variety of small-animal models have been used to study pertussis, none of them adequately reproduce the human disease (16). To address this gap, we recently developed a nonhuman primate model of pertussis using baboons (*Papio anubis*) and found the disease is very similar to severe clinical pertussis. Upon challenge, baboons experience 2 wk of heavy respiratory colonization and leukocytosis peaking between 30,000–80,000 cells/mL, similar to the range in pertussis-infected infants (1, 17). In addition, baboons experience a paroxysmal cough illness characterized by repeated fits of 5–10 coughs. The coughing fits last on average >2 wk in the baboon, although this is less than some severely infected children, where the cough can last up to 12 wk (1, 17). We also characterized airborne transmission of *B. pertussis* from infected to naïve animals, which is the route of transmission postulated to occur between humans (18). Because this is the only model of pertussis to reproduce the cough illness and transmission of the human disease, we believe it provides the unique opportunity to test our hypothesis that aP vaccines fail to prevent *B. pertussis* colonization, thus enabling transmission

Lapidot and Gill *Tropical Diseases, Travel Medicine and Vaccines* (2016) 2:26
DOI 10.1186/s40794-016-0043-8

Tropical Diseases,
Travel Medicine and Vaccines

REVIEW Open Access

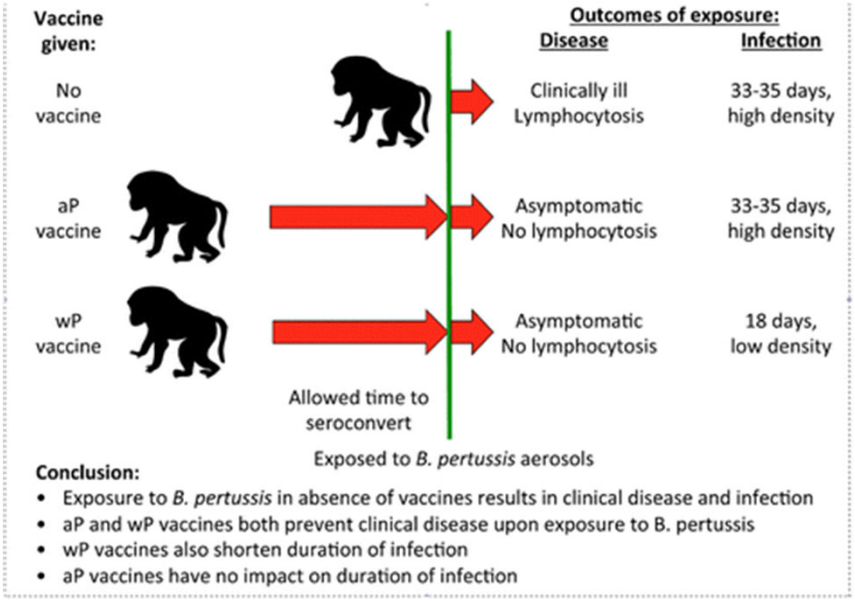
The Pertussis resurgence: putting together the pieces of the puzzle

Rotem Lapidot[1] and Christopher J. Gill[2,3*]

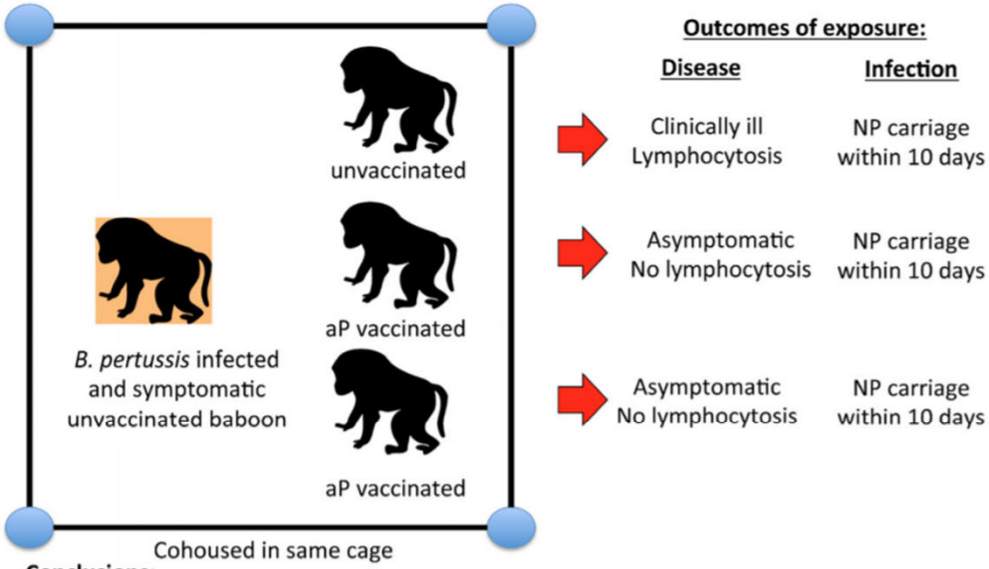
Abstract

Pertussis incidence is rising in almost every country where acellular pertussis (aP) vaccines have been introduced, and is occurring across all age groups from infancy to adulthood. The key question is why? While several known factors such as waning of immunity, detection bias due to more sensitive tests and higher awareness of the disease among practitioners, and evolutionary shifts among *B. pertussis* all likely contribute, collectively, these do not adequately explain the existing epidemiologic data, suggesting that additional factors also contribute. Key amongst these is recent data indicating that the immune responses induced by aP vaccines differ fundamentally from those induced by the whole cell pertussis (wP) vaccines, and do not lead to mucosal immunity. If so, it appears likely that differences in how the two categories of vaccines work, may be pivotal to our overall understanding of the pertussis resurgence.

Keywords: Pertussis, Acellular pertussis vaccine, Resurgence, Epidemiologic modeling, Asymptomatic transmission, Pertussis vaccines, Review



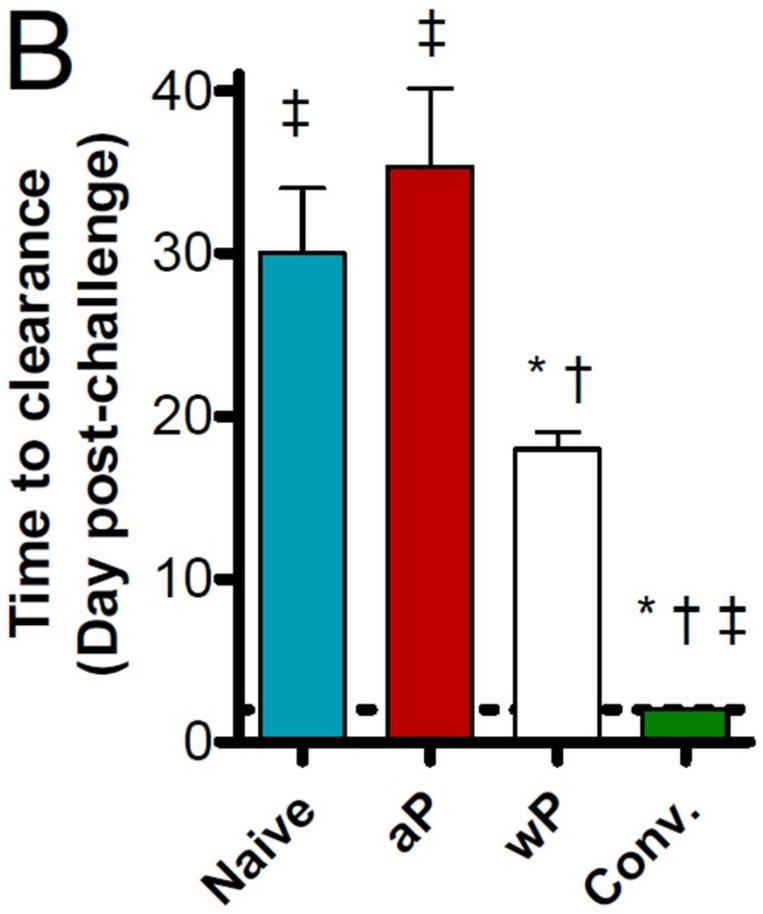
AEROSOL EXPOSURE



Conclusions:

- Unvaccinated infected animals easily transmit *B. pertussis*
- Unvaccinated animals who are exposed to infected animals also become infected
- aP vaccinated animals are resistant to clinical disease
- However, aP vaccination does not prevent these animals from being infected

Fig. 3 Outcome of exposure to infected animal by vaccination status. Here, an infected unvaccinated animal was co-housed with three initially uninfected animals, one of which was unvaccinated, while the other two had received aP vaccinations. All three animals became infected based on nasopharyngeal sampling, though only the unvaccinated animal showed signs of clinical illness. This showed that infection due to exposure to an infected animal can transmit *B. pertussis* (a more realistic model than exposure to aerosols). But again, while aP vaccinations blocked clinical disease, they did not prevent infection



PERTUSSIS VACCINATION

- Does not lead to mucosal immunity
- Does not prevent infection
- Does not prevent transmission
- Linked epitope suppression is the most likely explanation

Original Antigenic Sin

May 15, 1958
N Engl J Med 1958; 258:1016-1017
DOI: 10.1056/NEJM195805152582014

Although numerous strains of influenza viruses may cause clinically indistinguishable forms of "grippe," the various agents may be reduced by serologic technics to two important types of virus, the influenza A's and their relatives, the B's; and two branches that are "country cousins," the C's and D's. Within the first two ancestral clans are perhaps a dozen or so families of the A strain and four or so major variants of B strains. Such genotypic distinctions are of more than academic interest since immunity established after infection by one type in no way protects against infection at a subsequent date . . .

The Journal of Immunology

Original Antigenic Sin Responses to Influenza Viruses[1]

Jin Hyang Kim, Ioanna Skountzou, Richard Compans, and Joshy Jacob[2]

Most immune responses follow Burnet's rule in that Ag recruits specific lymphocytes from a large repertoire and induces them to proliferate and differentiate into effector cells. However, the phenomenon of "original antigenic sin" stands out as a paradox to Burnet's rule of B cell engagement. Humans, upon infection with a novel influenza strain, produce Abs against older viral strains at the expense of responses to novel, protective antigenic determinants. This exacerbates the severity of the current infection. This blind spot of the immune system and the redirection of responses to the "original Ag" rather than to novel epitopes were described fifty years ago. Recent reports have questioned the existence of this phenomenon. Hence, we revisited this issue to determine the extent to which original antigenic sin is induced by variant influenza viruses. Using two related strains of influenza A virus, we show that original antigenic sin leads to a significant decrease in development of protective immunity and recall responses to the second virus. In addition, we show that sequential infection of mice with two live influenza virus strains leads to almost exclusive Ab responses to the first viral strain, suggesting that original antigenic sin could be a potential strategy by which variant influenza viruses subvert the immune system. ***The Journal of Immunology,*** **2009, 183: 3294–3301.**

Influenza is the most recurring respiratory disease in humans. During the 20th century, influenza A viruses have afflicted the human race with three pandemics in 1918, 1957, and 1968, and numerous seasonal epidemics (1–3). Every year in the United States, 5–20% of the population gets infected with influenza viruses leading to over 200,000 hospitalizations and 36,000 deaths (4). Although a single influenza infection provides lifelong immunity against the homotypic strain, the public remains susceptible to infection with a novel flu variant (5). This is because the virus constantly undergoes genetic variation to avoid protective viruses that can no longer be neutralized by previous Abs (11). As a result, the variant viruses maintain shared epitopes with the parental strain but also have unique epitopes that allow escape from neutralizing Abs. When an immune host is exposed to this variant influenza virus, two things need to happen to ensure a successful protection: 1) activation of memory B cells that recognize shared epitopes and 2) activation of naive B cells that recognize novel epitopes. In the case of repeated infection with variant influenza viruses, the latter response is not induced and this phenomenon is called original antigenic sin. Original antigenic sin was first dis-

- "Humans, upon infection with a novel influenza strain, produce Abs against older viral strains at the expense of responses to novel, protective antigenic determinants"

Jin Hyang Kim, Ioanna Skountzou, Richard Compans, and Joshy Jacob[2]

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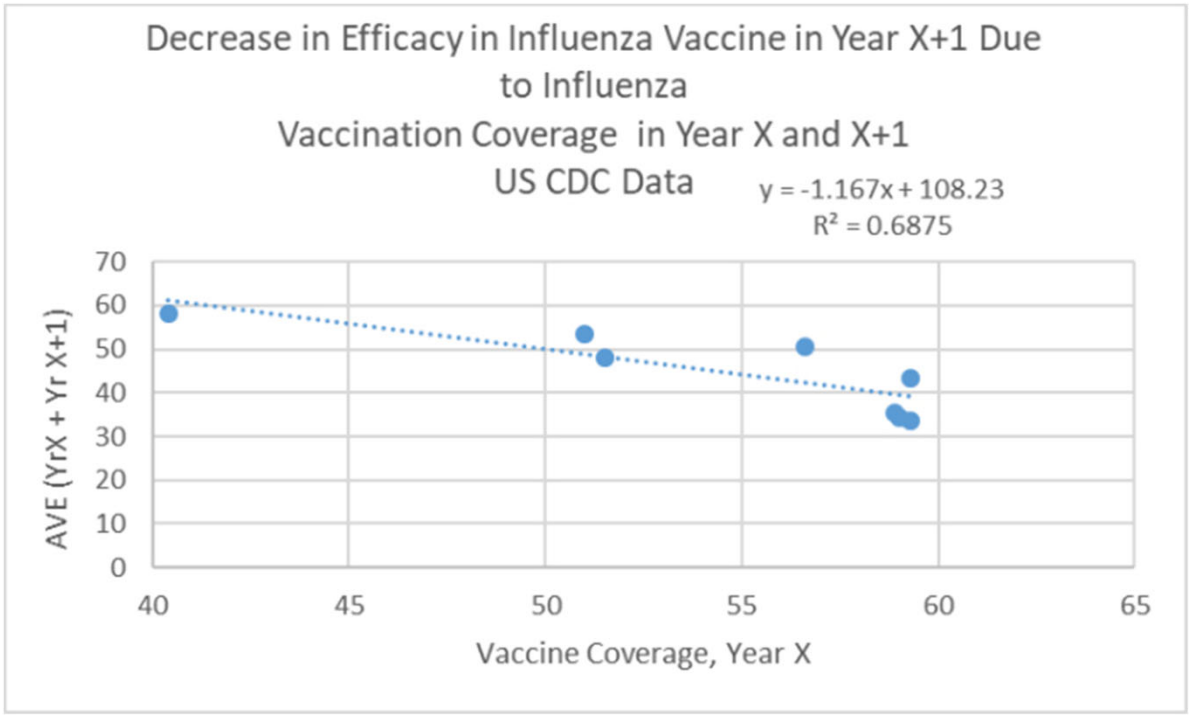
INFLUENZA VACCINE UPTAKE DECREASES EFFICACY OF FLU VACCINE… !!!

- JLW RESULT
- IPAK
- THIMEROSAL?
  NON-INFLUENZA "FLU"?
- "FLU-SYNDROME"



Epidemic Pertussis and Acellular Pertussis Vaccine Failure in the 21st Century

James D. Cherry, MD, MSc

In this issue of *Pediatrics* Acosta et al[1] present a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) vaccine effectiveness study in adolescents in Washington State during the first 6 months of 2012. Their findings support the previous Tdap effectiveness data from Wisconsin.[2] The duration of Tdap effectiveness is disappointing, particularly because case-control studies tend to inflate efficacy.[3]

In 4 recent publications (including 1 article in *Pediatrics*) I have discussed

because of clear evidence of "observer bias" in both studies.[10] In this present Washington State study, which involved adolescents 11 to 18 years of age, 81% of whom had received Tdap vaccines, the attack rate during the epidemic was only 182.3 per 100 000 for the one-half-year study period.[1] This rate is no greater than that noted during nonepidemic periods in the pre-DTaP and -Tdap eras.[8,9]

In 2012 in *Pediatrics* I discussed why pertussis vaccines fail[4]; however, new

Department of Pediatrics, David Geffen School of Medicine

POPULATION-WIDE IMMUNODEFICIENCY

NATURAL IMMUNITY	VACCINE IMMUNITY
TH1/TH2 BALANCE	TH2 SKEW
EXACT MATCH ANTIBODY TO ANTIGEN	INEXACT MATCH (ANTIBODY TO ANTIGEN)
LONG-TERM (LIFELONG)	SHORT-TERM
PASSIVE IMMUNITY	NO PASSIVE IMMUNITY
NO VACCINE FAILURE	ORIGINAL ANTIGENIC SIN
	VACCINE FAILURE
	METALS IMMUNODEFICIENCY

Senator Richard Pan California, Earlier This Month

CONCLUSIONS

Whole-population vaccination may be causing immunodeficiency that can be detected at the national level as increased unnecessary infections from vaccine-targeted and non-vaccine targeted pathogens.

Vaccination therefore cannot be expected to “protect” the immunodeficient.

In the long run, whole-population vaccination makes the use of vaccines **a self-defeating prospect** due to vaccine-induced immunodeficiency.

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