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Methods

Main Page
Methods

• Data Sources
• Changepoint Analysis
• Diagnostic and Statistical Manual
• Thimerosal Containing Vaccines
Methods

Data Sources

• For the US, autistic disorder data were obtained from the California Department of Developmental Services (DDS) [1] [2] [3] and from the Individuals with Disabilities Education Act (IDEA) program website of the Department of Education [4].

• Live birth data were extracted from the CDC’s “Annual reports of Vital Statistics of the United States”, [5] [6] and birth year AD prevalence per 10,000 was then calculated.

• Male population data were obtained from the U.S. Census Bureau website, [7] for data prior to 2000 and from the “factfinder” web site for data after 2000 [8]. Birth rates by age of father were obtained from the National Vital Statistics Reports: “Birth Final Data” [9].

• MMR, Varicella and Hepatitis A immunization coverage for children 19 to 35 months of age was obtained from the CDC National Immunization Survey (NIS) [10].
Changepoint Analysis

• Linear regression and $R^2$ analyses were used to assess correlations between AD prevalence and vaccine coverage or births by paternal age; associations with $P<0.05$ were considered significant.

• For CP determination, both the hockey-stick [1] and segmented line fitting [2] methods were employed. The robustness of our algorithm was tested by repeating the algorithm using deliberately chosen poor initial inputs.
Diagnostic and Statistical Manual

• Diagnostic and Statistical Manual (DSM) editions were checked for printing dates, found on the copyright page. This information was used as an indication of the rapidity with which changes in diagnostic criteria were embraced by the professional community. To determine whether DSM revisions might be related to changes in AD diagnosis rates, we predicted a range of AD changepoint birth years based on the printing dates for the various DSM revisions.

• Our assumptions were that the earliest age of autism diagnosis is 3 years and that by 8 years of age diagnosis is stable; therefore, a DSM revision would be predicted to induce a changepoint between 8 years prior to the earliest print date and 3 years prior to the latest print date. [1] [2].
Thimerosal Containing Vaccines

• A historical analysis of TCVs was conducted to determine the years in which changes to the thimerosal load received by vaccinated children occurred. Assuming that increased thimerosal load is related to AD we predicted AD changepoints based on FDA approval of new vaccines or new dosing schedules of TCVs and compared these predicted changepoint ranges to the actual calculated changepoints for AD.
THE UNITED STATES
(Click on the graphs under each topic)

AD Rate
3 yr olds  8 yr olds

AD Changepoints
Individual BYr
Combined Data

Vaccines
MMR
Varicella
Polio
Hep A
All vaccines

Paternal Age

Thimerosal

Diagnostic Substitution
Criteria
Schedules

Newschaffer
AD Prevalence for All States for 8 year olds Born Between 1992-2002
AD Prevalence for All States for 3 year olds Born between 1997-2007

Birth Year

AD prevalence (per 10,000)
Calculated AD Changepoints

US 1973 - 1987, 19 yr olds 1980.8
CA 1991 - 2002, 4 yr olds 1995.6
AD Changepoints

US 1973 - 1987, 19 yr olds  1980.8
CA 1970 - 1997, 5 yr olds   1980.9
CA 1991 - 2002, 4 yr olds   1988.4

POLIO VACCINES

(Click on the graphs under each topic)

- **TABLE OF POLIO VACCINES**

- **POLIO VACCINES AND AD CHANGEPOINTS**
# POLIO VACCINES IN US

<table>
<thead>
<tr>
<th>Cells</th>
<th>Notes</th>
<th>Company</th>
<th>FDA Approval</th>
<th>End year</th>
<th>Trade Name</th>
<th>Age of immunization</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC-5</td>
<td>OPV</td>
<td>Pfizer</td>
<td>1972</td>
<td>1976</td>
<td>DIPLOVAX</td>
<td>6-12 weeks</td>
<td>never caught on among U.S. pediatricians</td>
</tr>
<tr>
<td>IPV</td>
<td>Sanofi-Pasteur</td>
<td>11/20/1987</td>
<td>1991</td>
<td></td>
<td>POLIOVAX</td>
<td>2,4,6, 15-18 months</td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td></td>
<td>2008</td>
<td>Now</td>
<td></td>
<td>PENTACEL</td>
<td>2,4,6, 15-18 months</td>
<td></td>
</tr>
<tr>
<td>Vero cell line *</td>
<td>IPV</td>
<td>Sanofi-Pasteur</td>
<td>12/21/1990</td>
<td>Now</td>
<td>IPOL</td>
<td>2, 4, 6 -18 months, and 4-6 years</td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td>GSK</td>
<td>12/13/2002</td>
<td>Now</td>
<td></td>
<td>PEDIARIX</td>
<td>2, 4, 6 months</td>
<td></td>
</tr>
</tbody>
</table>

* The *Vero* lineage was isolated from kidney epithelia cells extracted from an African green monkey
POLIO VACCINES

<table>
<thead>
<tr>
<th>Cells</th>
<th>Notes</th>
<th>Company</th>
<th>FDA Approval</th>
<th>End year</th>
<th>Trade Name</th>
<th>Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC-5</td>
<td></td>
<td>Pfizer</td>
<td>1972</td>
<td>1976</td>
<td>DIPLOVAX</td>
<td>6-12 weeks</td>
<td>never caught on among U.S. pediatricians</td>
</tr>
<tr>
<td>OPV</td>
<td></td>
<td>1972</td>
<td>1976</td>
<td></td>
<td>DIPLOVAX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td>Sanofi-Pasteur</td>
<td>11/20/1987</td>
<td>1991</td>
<td></td>
<td>POLIOVAX</td>
<td>2,4,6, 15-18 months</td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td></td>
<td>2008</td>
<td></td>
<td></td>
<td>PENTACEL</td>
<td>2,4,6, 15-18 months</td>
<td></td>
</tr>
</tbody>
</table>


POLIOVAX

Prevalence per 10,000
Birth Year

B. Immunogenicity Review of Pentacel from FDA

BLA STN # 103940 (POLIOVAX), approved November 20, 1987

C. CDC list of Discontinued Vaccine in US


Poliovax was used from 1988-1991

D. Procedure of manual school immunization - Department of Health


- Trivalent Oral Polio Vaccine - June 25, 1963
- e-IPV - December 22, 1987
- IPV - Used from 1959-1989

- Poliovax - polio virus vaccine, enhanced, inactivated vaccine (e-IPV), Pasteur-Merieux- Connaught (discontinued 1991)

- Meruvax II: 1979.66
- MMR II: 1989.3
- Varivax: 1996.6
- MMR II 2nd dose: ~doubled
Measles, Mumps and Rubella

(Click on the graphs under each topic)

• MMR vaccine information table

• MMR and AD changepoints
## MEASLES, MUMPS, RUBELLA, VARICELLA

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Description</th>
<th>Manufacturer</th>
<th>Age Requirement</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/1979</td>
<td>Meruvax II</td>
<td>A rubella vaccine with the RA 27/3</td>
<td>Merck</td>
<td>&gt;=12 months</td>
<td>Licensed</td>
</tr>
<tr>
<td>1979</td>
<td>MMR II</td>
<td>Combined measles, mumps and rubella with the RA 27/3 strain</td>
<td>Merck</td>
<td>&gt;=12 months</td>
<td>Licensed</td>
</tr>
<tr>
<td>1989</td>
<td>MMR II</td>
<td>Combined measles, mumps and rubella with the RA 27/3 strain</td>
<td>Merck</td>
<td>&gt;=12 months</td>
<td>2nd dose</td>
</tr>
</tbody>
</table>
### MEASLES, MUMPS, RUBELLA, VARICELLA

**01/1979**  
**Meruvax II**  
A rubella vaccine with the RA 27/3  
Merck  
$\geq$12 months  
Licensed.

**1979**  
**MMR II**  
Combined measles, mumps and rubella with the RA 27/3 strain  
Merck  
$\geq$12 months  
Licensed

**1989**  
**MMR II**  
Combined measles, mumps and rubella with the RA 27/3 strain  
Merck  
$\geq$12 months  
2nd dose


![Graph showing prevalence of autism over birth years with data points for Meruvax II and MMR II vaccinations.](image-url)
Varicella

(Click on the graphs under each topic)

• Uptake of Varicella for All States for 35 months old born between 1992 through 2007

• U.S. AD vs Varicella for 8 years old born between 1992-1998

• All States AD vs Varicella for 8 years old born between 1993-1998

• Normalized Varivax immunizations vs Normalized Autism Disorder cases for 8 year olds for birth year 1993-1998

• Varicella vaccine and AD Changepoint
Varicella main page  Go Back to Main Page

Hep A recommended/considered in 17 states
U.S. AD vs Varicella for 8 years old born between 1992-1998

\[ R^2 = 0.9598 \]
Varivax immunizations plotted against Autism Disorder cases for 8 year olds for birth year 1993-1998

$R^2 = 0.8774$
Normalized Varivax immunizations plotted against Normalized Autism Disorder cases for 8 year olds for birth year 1993-1998

R² = 0.8328
**VARICELLA**

3/17/1995 Varivax Varicella virus vaccine, live Merck >=12 months Licensed


- 1979.66
- 1989.3
- 1996.6
Hepatitis A

(Click on the graphs under each topic)

• Table of Hepatitis A vaccines approved in the US.

• Hepatitis A immunization coverage for 35 months old born between 2003-2008

• Hepatitis A immunization case vs AD cases for children born 2003-2008
## History of Hepatitis A vaccines approved for use in the U.S.

<table>
<thead>
<tr>
<th>Date</th>
<th>Vaccine</th>
<th>Description</th>
<th>Manufacturer</th>
<th>Age Limit</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/22/1995</td>
<td>Havrix</td>
<td>The first inactivated hepatitis A vaccine</td>
<td>SmithKline Beecham</td>
<td>&gt;=24 months</td>
<td>Licensed</td>
</tr>
<tr>
<td>3/29/1996</td>
<td>Vaqueta</td>
<td>A second inactivated hepatitis A vaccine</td>
<td>Merck</td>
<td>&gt;=24 months</td>
<td>Licensed</td>
</tr>
<tr>
<td>5/11/1999</td>
<td>Twinrix</td>
<td>A combined hepatitis A inactivated and hepatitis B (recombinant) vaccine</td>
<td>SmithKline Beecham</td>
<td>&gt;=18 years</td>
<td>Licensed</td>
</tr>
<tr>
<td>8/11/2005</td>
<td>Vaqueta</td>
<td>A second inactivated hepatitis A vaccine</td>
<td>Merck</td>
<td>&gt;=12 months</td>
<td>FDA approved lowering the age limit to 12 months</td>
</tr>
<tr>
<td>10/18/2005</td>
<td>Havrix</td>
<td>The inactivated hepatitis A vaccine</td>
<td>GSK</td>
<td>&gt;=12 months</td>
<td>FDA approved lowering the age limit to 12 months</td>
</tr>
<tr>
<td>3/28/2007</td>
<td>Twinrix</td>
<td>A combined hepatitis A inactivated and hepatitis B (recombinant) vaccine</td>
<td>GSK</td>
<td>&gt;=18 years</td>
<td>FDA approved an accelerated dosing schedule.</td>
</tr>
</tbody>
</table>
Hep A immunization cases and AD cases for 3 year old children born between 2003-2008

Number of children immunized

Number of AD cases

R² = 0.6762
Paternal Age

(Click on the graphs under each topic)

• Absolute Live births and AD cases grouped by age of father from 1992-2002

• Absolute live births from 1960-2008 grouped by paternal age

• AD prevalence & live births to fathers aged 40 – 44 from 1960 to 2002
Absolute live births and AD cases grouped by age of father from 1992-2002
AD prevalence & live births to fathers aged 40 – 44 from 1960 to 2002
# Thimerosal containing vaccines and national vaccination schedule from 0-18 months

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Age / Thimerosal Containing Vaccine(µg/s)</th>
<th>Range of Potential thimerosal amount (µg/s)</th>
<th>Predicted BYr CP based on thimerosal introduction</th>
<th>Calculated BYr CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Birth</td>
<td>DTP (25)</td>
<td>100</td>
<td>none</td>
<td>1980.85</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100</td>
<td>none</td>
<td>1980.85</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>112.5-125</td>
<td>1988-1990</td>
<td>1988.4</td>
</tr>
<tr>
<td>1991-1993</td>
<td>DTP (25)</td>
<td>100</td>
<td>50-100**</td>
<td>1990-1993</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>150-200</td>
<td>1990-1993</td>
<td>1988.4</td>
</tr>
<tr>
<td>1994 - 1999</td>
<td>DTP (25)</td>
<td>100</td>
<td>0-100***</td>
<td>1994</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>137.5-237.5</td>
<td>1994</td>
<td>1995.6</td>
</tr>
</tbody>
</table>

*Hib (12.5-25)*

**Hib (0-25)**

***Hep B (12.5)***

Go Back to Main Page
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Social Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g. Pervasive lack of responsiveness to other people</td>
<td>3 examples/ Requirement not listed</td>
<td>1 example/ 1 required</td>
<td>5 examples/ 2 required</td>
<td>4 examples/ 2 required</td>
</tr>
<tr>
<td>Impaired Communication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g. Marked abnormalities in the production of speech, including volume, pitch, stress, rate, rhythm, and intonation; stereotyped and repetitive use of language or idiosyncratic language</td>
<td>1 example/ 1 required</td>
<td>4 examples/ Requirement not listed</td>
<td>6 examples/ 1 required</td>
<td>4 examples/ 1 required</td>
</tr>
<tr>
<td>Atypical or withdrawn behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g. Stereotyped body movements (for example, hand flicking or twisting, spinning, head-banging, complex whole-body movements)</td>
<td>1 example/ 1 required</td>
<td>2 examples/ Requirement not listed</td>
<td>5 examples/ 1 required</td>
<td>4 examples/ 1 required</td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before puberty</td>
<td></td>
<td>Before 30 months</td>
<td>Before 36 months unless specified</td>
<td>Before 36 months</td>
</tr>
<tr>
<td>Alternative diagnosis that must be excluded</td>
<td>Schizophrenia symptoms</td>
<td>None listed</td>
<td>None listed</td>
<td>Rett’s disorder* or childhood disintegrative disorder</td>
</tr>
<tr>
<td></td>
<td>Date of printing</td>
<td>Number printed</td>
<td>Predicted BYr CP range by DSM printings</td>
<td>Calculated BYr CP</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>DSM III</strong></td>
<td>Feb-80</td>
<td>40,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May-80</td>
<td>25,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sep-80</td>
<td>25,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nov-80</td>
<td>30,000</td>
<td>Feb 1972-Sep 1978</td>
<td>1980.85*</td>
</tr>
<tr>
<td></td>
<td>Jan-81</td>
<td>30,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mar-81</td>
<td>35,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sep-81</td>
<td>25,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DSM IIIR</strong></td>
<td>May-87</td>
<td>75,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jun-87</td>
<td>80,000</td>
<td>May 1979 –Nov 1984</td>
<td>1988.4</td>
</tr>
<tr>
<td></td>
<td>Nov-87</td>
<td>75,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DSM IV</strong></td>
<td>May-94</td>
<td>not given</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jul-94</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Jan-95</td>
<td>not given</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
National Autism Prevalence Trends From United States Special Education Data
Craig J. Newschaffer, Matthew D. Falb and James G. Gurney
