Vaccines: Successes, Failures, Resistance, and Unexpected Benefits

10 October 2015
Tony Moody MD
Duke Pediatric Infectious Diseases

Image obtained from the Library of Congres, WPA Poster Project.
Disclosures

• Advisory board member for GSK (for belimumab pregnancy registry).

• Co-founder of Grid Therapeutics (formerly Cue Biologics).

• Chief Medical Officer, DHVI.
or How I Learned to Stop Worrying and Love the Shot
Educational Objectives

• Describe the stages of vaccine development.

• Recognize the benefits and potential risks of vaccines.

• Describe some of the reasons for vaccine hesitancy.
Vaccine-Preventable Deaths

2001 WHO Estimates

global actual / global prevented

diphtheria  5,000  /  73,000
pertussis   301,000 /  1 million
measles    676,000 /  1.2 million
Hib        463,000 /  5,000
What have we done wrong?

1. Child mortality very low in US
2. Lack of understanding?
3. Failure to appreciate risk
4. Correlation = causation?
Cotton Mather (1663-1728)

Boston 1721
smallpox epidemic

Onesimus (slave)
variolation

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center
Definitions

**variolation** *n*
inoculation with smallpox material
derived from the Latin
**variola** (pox / pustule)
Cotton Mather (1663-1728)

Boston 1721
smallpox epidemic

Onesimus (slave)
variolation

Dr. Zabdiel Boylston
son + two slaves

death rate
1:12 → 1:40

Image courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center
Mr. Maitland's
ACCOUNT
OF
INOCULATING
THE
SMALL POX
Vindicated,
From Dr. Wagstaffe's Misre-
presentations of that Pra-
tice, with some Remarks
on Mr. Maffey's Sermon.

LONDON:
Printed and Sold by J. Pelle, at Locke's
Head in Paternoster-Row. 1732.
Edward Jenner (1749-1823)

investigated claims of immunity after cowpox

Image courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center
Image courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center
Definitions

vaccination $n$
the act of administering material to induce or increase specific immunity

derived from the Latin
vacca (cow)
Edward Jenner (1749-1823)

investigated claims of immunity after cowpox

1796: vaccinated James Phipps (8yo)

subsequently challenged with smallpox
Louis Pasteur (1822-1895)

developed principle of attenuation

developed attenuated rabies vaccine

post-exposure vaccination of Joseph Meister (1885)
Emile Roux (1853-1933)

physician working with
L Pasteur

refused to inoculate
J Meister

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center
Three eras of vaccine development
First era

Anti-bacterial vaccines
CARRIER OF

DIPHTHERIA

KEEP OUT OF THIS HOUSE

By Order of BOARD OF HEALTH

Any person removing this card without authority is liable to prosecution

HEALTH OFFICER.
Emil von Behring (1854-1917)


Paul Ehrlich (1854-1915)

WE can do likewise

HOW TORONTO BEAT DIPHTHERIA

1929
Cases: 1022  Deaths: 64

CAMPAIGN FOR IMMUNISATION BEGINS

1933
56  5

1940
No Cases

it's up to you!

Image obtained from the National Library of Medicine, History of Medicine Collection
B pertussis—epidemiology

Until the mid 1940s, accounted for more deaths in children less than one year old than measles, scarlet fever, diphtheria, poliomyelitis and meningitis combined
Albert Calmette  (1863-1933)

Camille Guérin  (1872-1961)

Image courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center

Image obtained via en.wikipedia.org
Timeline of Vaccines

1879: cholera
1885: rabies
1890: tetanus
1896: typhoid fever
1897: bubonic plague

1921: diphtheria
1925: tuberculosis
1926: scarlet fever
1927: pertussis
Second era

Cell culture leading to anti-virus vaccines
John Enders (1897-1985)

developed tissue culture techniques to grow viruses

1954 Nobel Prize with Thomas Weller and Frederick Robbins

Image from Nobel.org via Wikipedia
Image via Wikipedia
Originally from Deutsches Grünes Kreuz

"Wellbee" says
BE WELL!

ORAL
VACCINE

• tastes good
• works fast
• prevents polio

Image obtained from
the CDC Public Health Image Library
THE CUTTER INCIDENT

POLIOMYELITIS FOLLOWING FORMALDEHYDE-INACTIVATED POLIOVIRUS VACCINATION IN THE UNITED STATES DURING THE SPRING OF 1955

II. RELATIONSHIP OF POLIOMYELITIS TO CUTTER VACCINE

BY

NEAL NATHANSON AND ALEXANDER D. LANGMUIR

(Received for publication March 12, 1963)
Polio vaccine

The Cutter Incident

>380,000 doses of Cutter vaccine
>300,000 school clinics
~120,000 from “high rate lots”

initial paralysis in inoculated limb
Polio vaccine

The Cutter Incident

vaccine given between
13 – 27 April 1955
est. 40,000 infections
51 paralyzed / 5 deaths
89 family contacts paralyzed
5 family contacts died
Figure 1. Cutter-associated cases by onset.

Immunopathogenesis of vaccine-enhanced RSV disease

Peter J.M. Openshaw*, Fiona J. Culley, Wieslawa Olszewska

Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College of Science, Technology and Medicine at St. Mary's, Norfolk Place, London W2 1PG, UK
RSV vaccine

Formalin-Inactivated RSV Vaccine

1966-1967 trial

children 2 mos to 9 yrs

good rise in Ab titers
during subsequent season

80% of vaccinees hospitalized

(2)

5% of controls (0)
RSV vaccine

Formalin-Inactivated RSV Vaccine

skewing of T cell responses

overactive pulmonary immune responses
Timeline of Vaccines

1932: yellow fever
1937: typhus
1945: influenza
1952: polio (Salk)
1954: Japanese encephalitis
1954: anthrax
1962: polio (Sabin)
1963: measles
1967: mumps
1970: rubella
1974: chicken pox
Third era

Molecular biology
Timeline of Vaccines

1977: *Streptococcus pneumoniae*
1978: *Neisseria meningitidis*
1981: hepatitis B
1985: *Haemophilus influenzae* type b (HiB)
Problems in the 1980/90s

Hepatitis B vaccine derived from sera of infected persons (HIV-1 risk).

Polysaccharide vaccines associated with poor response in infants.
Rotavirus vaccine

RotaShield®

licensed 1998

increased cases of intussusception

pulled from market in 1999
FDA NEWS RELEASE

For Immediate Release: March 22, 2010

Media Inquiries: Shelly Burgess, 301-796-4651; shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Components of Extraneous Virus Detected in Rotarix Vaccine; No Known Safety Risk

FDA Recommends Clinicians Temporarily Suspend Use of Vaccine as Agency Learns More
Rotavirus vaccine

Rotarix®: GSK rotavirus vaccine has DNA from porcine circovirus 1 always had it, even in safety trials voluntary suspension
Rotavirus vaccine

Porcine circovirus 1

infests swine,
causes no known disease

no known circoviruses infecting humans
Vaccine Contaminants

Vaccines are sometimes messy preparations.

Sometimes extra things get in the mix.
Timeline of Vaccines

1992: hepatitis A
1998: Lyme dz
1998: rotavirus
2003: LAIV
2006: HPV

1990: Hib cnjgt
1990: rHBV
2000: PCV7
2001: Men cnjgt
Fourth era?

Rational vaccine design?
customized pharmaceuticals
personalized vaccines
HLA-based vaccines
tetanus vaccine
influenza vaccine
rubella vaccine
sewer & sanitation
<table>
<thead>
<tr>
<th>Vaccine Against</th>
<th>Associated Genes</th>
<th>Observed Phenomenon</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (subunit)</td>
<td>$IL10$</td>
<td>Antibody titer increased (ACC haplotype)</td>
<td>(Hohler et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>$HLA-DRA$, $FOXP1$</td>
<td>Antibody titer (responder vs. non-responder)</td>
<td>(Davila et al., 2010)</td>
</tr>
<tr>
<td>HIV-1 (adenovirus vector)</td>
<td>$HLA-B$ (various alleles)</td>
<td>gag-specific CD8+ T cell response increased</td>
<td>(Fellay et al., 2011)</td>
</tr>
<tr>
<td>Influenza</td>
<td>$HLA-DQB1$</td>
<td>Hemagglutination inhibition titer increased</td>
<td>(Gelder et al., 2002)</td>
</tr>
<tr>
<td></td>
<td>$IL6$</td>
<td>Hemagglutination inhibition titer increased</td>
<td>(Poland et al., 2008)</td>
</tr>
<tr>
<td>Measles</td>
<td>$HLA-B$</td>
<td>Seroconversion after one immunization (high for *07, low for *08)</td>
<td>(Jacobson et al., 2003)</td>
</tr>
<tr>
<td>Mumps</td>
<td>$HLA-DQB1*0303$</td>
<td>Antibody titer decreased</td>
<td>(Ovsyannikova et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>$HLA-DRB1$, $HLA-DQA1$, $HLA-DQB2$, $IL10RA$, $IL12RB1$, $IL12RB2$</td>
<td>Lymphoproliferation (various effects)</td>
<td>(Ovsyannikova et al., 2008)</td>
</tr>
<tr>
<td>Pertussis (acellular)</td>
<td>$TLR4$ (and downstream genes)</td>
<td>Antibody titer increased</td>
<td>(Kimman et al., 2008)</td>
</tr>
<tr>
<td>Rubella</td>
<td>$IL12B$, $IFNGR1$</td>
<td>IFN-$\gamma$, IL-10 secretion (various effects)</td>
<td>(Jacobson et al., 2009)</td>
</tr>
<tr>
<td></td>
<td>$DDX58$, $RARB$, $TRIM5$, $TRIM22$</td>
<td>Antibody titer (various effects)</td>
<td>(Ovsyannikova et al., 2010b)</td>
</tr>
<tr>
<td></td>
<td>$DDX58$, $MAVS$, $RARB$, $TLR3$</td>
<td>IFN-$\gamma$, IL-6, TNF-$\alpha$ secretion (various effects)</td>
<td>(Ovsyannikova et al., 2010a)</td>
</tr>
</tbody>
</table>
Correlates of Protection
Correlates of Protection

It’s Antibody, except when it isn’t.
Fig. 3. Comparative levels of antibody to hepatitis A virus (HAV) after administration of immune serum globulin, one dose of an attenuated hepatitis A virus vaccine, three doses of an inactivated hepatitis A virus vaccine and natural infection. The detection limits of the hepatitis A virus antibody assay are \( \sim 100 \) mIU per ml. Reproduced with permission from the article of Feinstone and Gust.\(^{20}\)
<table>
<thead>
<tr>
<th>Test</th>
<th>% Seroconversion or Efficacy</th>
<th>Rubini</th>
<th>Jeryl Lynn</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>38</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>IFA</td>
<td>92</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>87</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Efficacy</td>
<td>6</td>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>
Final Thoughts 1/3

Bad studies, misinformation, & the tyranny of small numbers
Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine

**cohort**
- one pt w/ MS
- one pt w/o MS

**results**
six weeks after booster doses → demyelination

**characteristics**
both +ve for
- HLA DR2 & B7
Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study

**cohort**
Finland
- 128,936 unvaccinated
- 116,352 vaccinated

**characteristics**
Patient groups are from pre- and post-vaccine eras

**results**
Overall rates of DM 1 up
No correlation w/ vaccines

Subsequent letters
‘d the statistical methods and the data presentation
CHRONIC MERCURIALISM IN THE HATTERS’ FUR-CUTTING INDUSTRY

PAUL A. NEAL, M.D.
AND
R. R. JONES, M.D.
Passed Assistant Surgeons, United States Public Health Service
WASHINGTON, D. C.

JAMA 110(5) 337-343 (1938)
Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data


**cohort**
convergence of multiple Danish public healthcare databases

**characteristics**
incidence of autism

**results**
rates of autism went up after thimerosal was removed from vaccines
Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children


**cohort**
12 children w/ PDD
14 matched controls

**results**
nodular hyperplasia seen in PDD pts / not in ctls

**characteristics**
8 after measles vaccine
1 after measles infection
2 others immunized

methy]malonic acid excretion elevated
Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Limell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated with the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in one. All 12 children had intestinal abnormalities ranging from ileal lymphoid hyperplasia to malabsorption. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative personality (one), and possible cerebral palsy (two). There were no focal neurological abnormalities, hypoglycaemia, and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched control (10·5 mg/L) and haemoglobin in four children. Low growth in four children. Low fasting serum levels were found in five children.

Interpretation The identity associated gastrointestinal disease and developmental regression in a group of prevalent children, which is generally associated in time with possible environmental triggers.


See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield, A Anthony, J H Limell, A P Dhillon, S E Davies) and the University Departments of Paediatric Gastroenterology (S H Murch, D M Casson, M Malik, M A Thomson, J A Walker-Smith), Child and Adolescent Psychiatry (M Berelowitz), Neurology (P Harvey), and Radiology (A Valentine), Royal Free Hospital and School of Medicine, London NW3 2QG, UK

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and vomiting, and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consisting of a department of paediatric gastroenterology, had a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms, including abdominal pain, bloating, and food intolerance, which persisted. All children were admitted to the ward approximately by their parents.

Critical investigations

Clinical history, including details of vaccinations and dietary intake, was recorded, and the children were assessed. The historical form was obtained by the senior clinician. Neurological and psychiatric assessments were done by consultant staff (PH, MJ) with HAM-A criteria. Developmental delay was determined by a review of developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; an assessment had been conducted professionally elsewhere; these assessments were used as the main basis for their developmental diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM of MAU under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colon, and from the rectum. The procedure was recorded by video or still images, and there was compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal intestinal mucosa. Barium follow-through radiography was possible in some cases. A colonoscopy was performed with a colonoscope (MRM) providing visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thymus function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodevelopmental disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and the 14 age-matched and sex-matched normal controls, by a modification of a technique described previously. Chromatograms were scanned digitally on computer, and analysed the methylmalonic acid areas and controls. Methylmalonic acid concentrations in patients and controls were compared by a two-sample t test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antinuclear antibodies and extracts were screened for fragile-X if this had not been done.
Wakefield Retraction

February 2004

10 / 13 original authors retract

Wakefield working for Legal Aid Board

Wakefield named in patent for potential MMR competitor
Wakefield’s “autistic enterocolitis” under the microscope

Andrew Wakefield’s claims for a new bowel condition in autistic children have been largely overlooked in the furore over MMR vaccination. Brian Deer reports
Wakefield Retraction

April 2010 article

original paper
11/12 children with chronic “non-specific colitis”

original path reports
8/11 pathology reports normal
Final Thoughts 2/3

Can vaccines have off-target benefits?
Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis

Maria José de Castro,1 Jacobo Pardo-Seco,2,3 and Federico Martinón-Torres1,2

BCG Heterologous Protection in Children • CID 2015:60 (1 June) • 1611

A

Hospitalization rate (1/100,000)

Year

1997 1999 2001 2003 2005 2007 2009 2011

URTI/LRTI

A

Hospitalization rate (1/100,000)

Year

1997 1999 2001 2003 2005 2007 2009 2011

Sepsis
Randomized Trial of BCG Vaccination at Birth to Low-Birth-Weight Children: Beneficial Nonspecific Effects in the Neonatal Period?

Result

BCG given to LBW infants reduced all-cause mortality.

Figure 2. Cumulative mortality curves during the first year of life according to randomization group.
Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina,1,2* C. Jessica E. Metcalf,1,3 Rik L. de Swart,4 A. D. M. E. Osterhaus,4 Bryan T. Grenfell1,3

[Graphs showing trends in measles cases and non-measles deaths in England & Wales, United States, and Denmark.]
Final Thoughts 3/3

Are we the victims of our own success?
What have we done wrong?

1. Child mortality very low in US
2. Lack of understanding?
3. Failure to appreciate risk
4. Correlation $\neq$ causation?
Life Expectancy

The decrease in death rates over the 75 years varied by age.

Figure 3. Percentage change in death rates by age: United States, 1935–2010

NOTE: 2010 data are preliminary.

Herd Immunity

Herd Immunity

Herd Immunity

1. “I’m protected because others are vaccinated.”
2. “I won’t be exposed. / I am not going to travel to an endemic area.”
3. “So what if I get sick.”
Risks of Infection

1. The world has shrunk.
2. Adult disease often associated with worse outcomes.
Correlation ≠ Causation

1. MMR and autism
2. Thimerosal and autism
3. HBV and multiple sclerosis
4. Hib and diabetes
Global Average Temperature vs. Number of Pirates

Number of Pirates (Approximate):
- 35000
- 45000
- 20000
- 15000
- 5000
- 400
- 17

Global Average Temperature, °C:
- 16.5
- 16.0
- 15.5
- 15.0
- 14.5
- 14.0
- 13.5
- 13.0

Year:
- 1820
- 1860
- 1880
- 1920
- 1940
- 1980
- 2000

Image from Wikipedia.
A new parameter for sex education

Sir—There is concern in West Germany over the falling birth rate. The accompanying graph\textsuperscript{1,2} might suggest a solution that every child knows makes sense.

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    xlabel=Year,
    ylabel=Pairs of brooding storks (cf),
    xmin=1965, xmax=1980,
    ymin=1000, ymax=2000,
    ytick={1000,1500,2000},
    legend style={at={(0.5,0.95)},anchor=north east},
    legend entries={Pairs of brooding storks, Millions of newborn babies}
]
\addplot coordinates{(1965,1) (1970,1.2) (1975,1.5) (1980,2.0)};\addlegendentry{Millions of newborn babies (s)}
\end{axis}
\end{tikzpicture}
\end{center}

Helmut Sies

Institut für Physiologische Chemie 1,
Universität Düsseldorf,
Moorenstrasse 5, D-4000 Düsseldorf,
FRG

A new parameter for sex education

Sir—There is concern in West Germany over the falling birth rate. The accompanying graph\textsuperscript{1,2} might suggest a solution that every child knows makes sense.

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    width=\linewidth,
    xlabel = Year,
    ylabel = Pairs of breeding storks (\cdot),
    y label style={at={(axis description cs:0,0.9)}, anchor=south,align=center},
    x label style={at={(axis description cs:0.95,0.5)}, rotate=90, anchor=north, align=right},
    ytick = {1, 1.5, 2},
    yticklabels = {1, 1.5, 2},
    grid = major,
    legend pos = north east,
]
\addplot[mark=o, color=blue, solid, error bars/.cd, y dir=both, y explicit, error mark options={scale=0.8}]
coordinates {
(1965, 2.0) +- (0, 0.2) 
(1970, 1.5) +- (0, 0.2) 
(1975, 1.0) +- (0, 0.2) 
(1980, 0.5) +- (0, 0.2)
};
\addplot[mark=*, color=red, solid, error bars/.cd, y dir=both, y explicit, error mark options={scale=0.8}]
coordinates {
(1965, 1.0) +- (0, 0.2) 
(1970, 0.75) +- (0, 0.2) 
(1975, 0.5) +- (0, 0.2) 
(1980, 0.25) +- (0, 0.2)
};
\legend{Pairs of breeding storks, Millions of newborn babies}
\end{axis}
\end{tikzpicture}
\end{center}

Helmut Sies

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