

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?



Image obtained from the MIT OpenCourseware site



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 $1:12 \rightarrow 1:40$

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

Mr. MAITLAND'S A C C O U N T OF

INOCULATING

THE

SMALL POX Vindicated,

From Dr. Wag staffe's Mifreprefentations of that PRAC-TICE, with fome Remarks on Mr. Massey's Sermon. Image obtained via the Lampeter Corpus of Early Modern English Tracts at Chemnitzin University, Germany



LONDON: Printed and Sold by J. PEELE, at Lock's Head in Paternofler-Row, 1722.



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

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



Image obtained from the National Library of Medicine



Louis Pasteur (1822-1895)

developed principle of attenuation

developed attenuated rabies vaccine

post-exposure vaccination of Joseph Meister (1885)

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



Emile Roux (1853-1933)

physician working with L Pasteur

> refused to inoculate J Meister

> > Directed and rectance areas

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

Three eras of vaccine development

First era

Anti-bacterial vaccines



Image obtained from the National Library of Medicine, History of Medicine Collection

Emil von Behring (1854-1917)



MacNalty A. Emil von Behring, born March 15, 1854 Br Med J 1(4863): 668–670 (1954).

Paul Ehrlich (1854-1915)



Dale H. Paul Ehrlich, born March 14, 1854 Br Med J 1(4863): 659–663 (1954).

can do likewise HOW TORONTO BEAT DIPHTHERIA Deaths Cases 1022 64 1929 CAMPAIGN FOR IMMUNISATION BEGINS 5 56 1955 No Cases it's up to you!

Image obtained from the National Library of Medicine, History of Medicine Collection

U



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)



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

Camille Guérin (1872-1961)



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 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 1, 2

ΈY

NEAL NATHANSON AND ALEXANDER D. LANGMUIR³

(Received for publication March 12, 1963)

Nathanson & Langmuir, Am J Hyg 78: 29-60 (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.

Nathanson & Langmuir, Am J Hyg 78: 29-60 (1963).



Image obtained from the CDC Public Health Image Library

Vaccine 20 (2002) S27-S31

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)



Formalin-Inactivated RSV Vaccine

skewing of T cell responses

overactive pulmonary immune responses

Timeline of Vaccines

1932: yellow fever 1962: polio (Sabin)

1974: chicken pox

- *1937: typhus* **1963: measles**
- 1945: influenza 1967: mumps
- 1952: polio (Salk) 1970: rubella
- 1954: Japanese encephalitis
- 1954: anthrax

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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



Murphy et al., N Engl J Med 344: 564-572 (2001).

FD U.S. Food and Drug Administration

Home > News & Events > Newsroom > Press Announcements

News & Events

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

infects 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

Vaccine Against	Associated Genes	Observed Phenomenon	Reference
Hepatitis B (subunit)	IL10	Antibody titer increased (ACC haplotype)	(Hohler et al., 2005)
	HLA-DRA, FOXP1	Antibody titer (responder vs. non-responder)	(Davila et al., 2010)
HIV-1 (adenovirus vector)	HLA-B (various alleles)	gag-specific CD8+ T cell response increased	(Fellay et al., 2011)
Influenza	HLA-DQB1	Hemagglutination inhibition titer increased	(Gelder et al., 2002)
	IL6	Hemagglutination inhibition titer increased	(Poland et al., 2008)
Measles	HLA-B	Seroconversion after one immunization (high for *07, low for *08)	(Jacobson et al., 2003)
Mumps	HLA-DQB1*0303	Antibody titer decreased	(Ovsyannikova et al., 2008)
	HLA-DRB1, HLA- DQA1, HLA-DQB2, IL10RA, IL12RB1, IL12RB2	Lymphoproliferation (various effects)	(Ovsyannikova et al., 2008)
Pertussis (acellular)	TLR4 (and downstream genes)	Antibody titer increased	(Kimman et al., 2008)
Rubella	IL12B, IFNGR1	IFN-γ, IL-10 secretion (various effects)	(Jacobson et al., 2009)
	DDX58, RARB, TRIM5, TRIM22	Antibody titer (various effects)	(Ovsyannikova et al., 2010b)
	DDX58, MAVS, RARB, TLR3	IFN- γ , IL-6, TNF- α secretion (various effects)	(Ovsyannikova et al., 2010a)



Adapted from Haynes et al. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. *Nat Biotechnol* **30(5):** 423–433 (2012). [PMC3512202]

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 ~100 mIU per ml. Reproduced with permission from the article of Feinstone and Gust.²⁰

SA Plotkin, Immunologic correlates of protection induced by vaccination. PIDJ 20: 63-75 (2001).

TABLE 6. Seroconversion to mumps and efficacy afterimmunization

${\operatorname{Test}}$	% Seroconversion or Efficacy	
	Rubini	Jeryl Lynn
ELISA	38	97
IFA	92	100
Neutralizing antibodies	87	74
Efficacy	6	62

SA Plotkin, Immunologic correlates of protection induced by vaccination. PIDJ 20: 63-75 (2001).

Final Thoughts 1/3

Bad studies, misinformation, & the tyranny of small numbers

Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine

Herroelen L, de Keyser J, Ebinger G. Lancet **338:** 1174-1175 (1991).

cohort

one pt w/ MS one pt w/o MS

characteristics

both +ve for HLA DR2 & B7

results

six weeks after booster doses \rightarrow demyelination

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

Karvonen M, Cepaitis Z, Tuomilehto J. BMJ 318: 1169-1172 (1999).

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



thimerosal / thiomersal



CHRONIC MERCURIALISM IN THE HATTERS' FUR-CUTTING INDUSTRY

PAUL A. NEAL, M.D.

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

Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner A-M, Andersen PH, Mortensen PB. *Pediatrics* **112:** 604-606 (2003).

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

Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. *Lancet* **351:** 637-641 (1998).

cohort

12 children w/ PDD 14 matched controls

characteristics

8 after measles vaccine 1 after measles infection

2 others immunized

results

nodular hyperplasia seen in PDD pts / not in ctls

methylmalonic 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 Linnell, 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. lleocolonoscopy 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 by the parents, with measles, mumps, and rub vaccination in eight of the 12 children, with meas infection in one child, and otitis media in a All 1 children had intestinal abnormalities rangin from lymphoid nodular hyperplasia to a noid u ration. Histology showed patchy chronic inflan ion in 11 children and reactive ilea mpho erplasia in seven, but no granulomas. Be gioural diso included autism (nine), disintegrativ sis (one), a ossible postviral or vaccinal encephalitis (o). There were no focal neurological ab malities and and EEG tests were normal. Abnormal laboratory results are significantly sthylmal acid compared with ageraised urinary .03), low haemoglobin in four matched control (p-) children, m IgA in ar children. low 5

Internation e idem of associated gastrointestinal dial se and ovelopmental regression in a group of previously amailtonic of, which was generally associated in time to possible environmental triggers.

Lancet 1995 151: 637-41 See Commentary page

Inflammatory Bowel Disease Study Croup, University Departments of Medicine and Histopathology (A J Wakeheld Facs, A Anthony Me, J Linnell Pea, A P Dhillon Macrain, S E Davies Mechae) and the University Departments of Paediatric Castroenterology (S H Murch Me, D M Casson Merz, M Malik Merz, M A Thomson Face, J AM Walker-Smith Face), Child and Adolescent Psychiatry (M Berelowitz Fachaec), Neurology (P Harvey Face), and Radiology (A Valentine Face), Reyal Face Hospital and School of Medicine, London NW3 2006, UK

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a per of apparent normality, lost acquired skills, including ication. 3 com They all had gastrointestinal mptoms, uding abdominal pain, diarrhoea, and some ating and, i cases, food intolerance. We moribe clinical fi lings, and gastrointestinal feature of these ch. en.

Patients and metric

red to the department of a him by of a pervasive accurced skills and intestinal red to 1 12 children, cons ativel a hi derology der with loss paediatric gastry developmental abdominal on, bloating and food symptoms 🦯 intolerance), were inv. pated. All children were admitted to the ward for neek, accomp ed by their parents.

nical investigations

took historie including details of immunisations and ensure to infect us diseases, and assessed the children. In 11 case the history are solutioned by the senior clinician (W-S). Neuron included a psychiatric assessments were done by possiliant suff (PH, MB) with HMS-4 criteria.¹ Developmental to is included a review of prospective developmental records from a rents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midaxolam and pethidine. Patred frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were 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 appearances in the terminal ileum. Bartum follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRD), electroencephalography (EBG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain faity acids, and cerebrospinal-fluid lactate were measured to exclude known curses of childhood neurodegenerative disease. Urinary methylimaionic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.² Chromatograms were scanned digitally on computer, to analyse the methylimaionic-acid zones from cases and controls. Urinary methylimaionic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric asay.

Children were screened for antiendomyseal antibodies and boys 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

Deer, BMJ 340: 838-841 (2010).

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

María José de Castro,¹ Jacobo Pardo-Seco,^{2,3} and Federico Martinón-Torres^{1,2}

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


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

Peter Aaby,^{1,2} Adam Roth,^{3,6} Henrik Ravn,³ Bitiguida Mutna Napirna,^{2,a} Amabelia Rodrigues,¹ Ida Maria Lisse,⁴ Lone Stensballe,³ Birgitte Rode Diness,¹ Karen Rokkedal Lausch,¹ Najaaraq Lund,¹ Sofie Biering-Sørensen,¹ Hilton Whittle,⁵ and Christine Stabell Benn^{1,3} JID 2011:204 (15 July) • 245



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. Grenfell^{1,3}

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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 = 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. SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Herd Immunity



Fine P, Eames K, Heymann DL. "Herd Immunity": A Rough Guide. Clin Infect Dis 52(7): 911–916 (2011).

Herd Immunity



Fine P, Eames K, Heymann DL. "Herd Immunity": A Rough Guide. Clin Infect Dis 52(7): 911–916 (2011).

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.
- 3. More immunocompromised persons.
- 4. "Nostalgia"—misremembered childhood disease.

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

Image from Wikipedia.

A new parameter for sex education

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



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

Sies, Nature 332: 495 (1988).

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