Imperial College London

# The importance of evidence in the practice of medicine

## 27th February 2012

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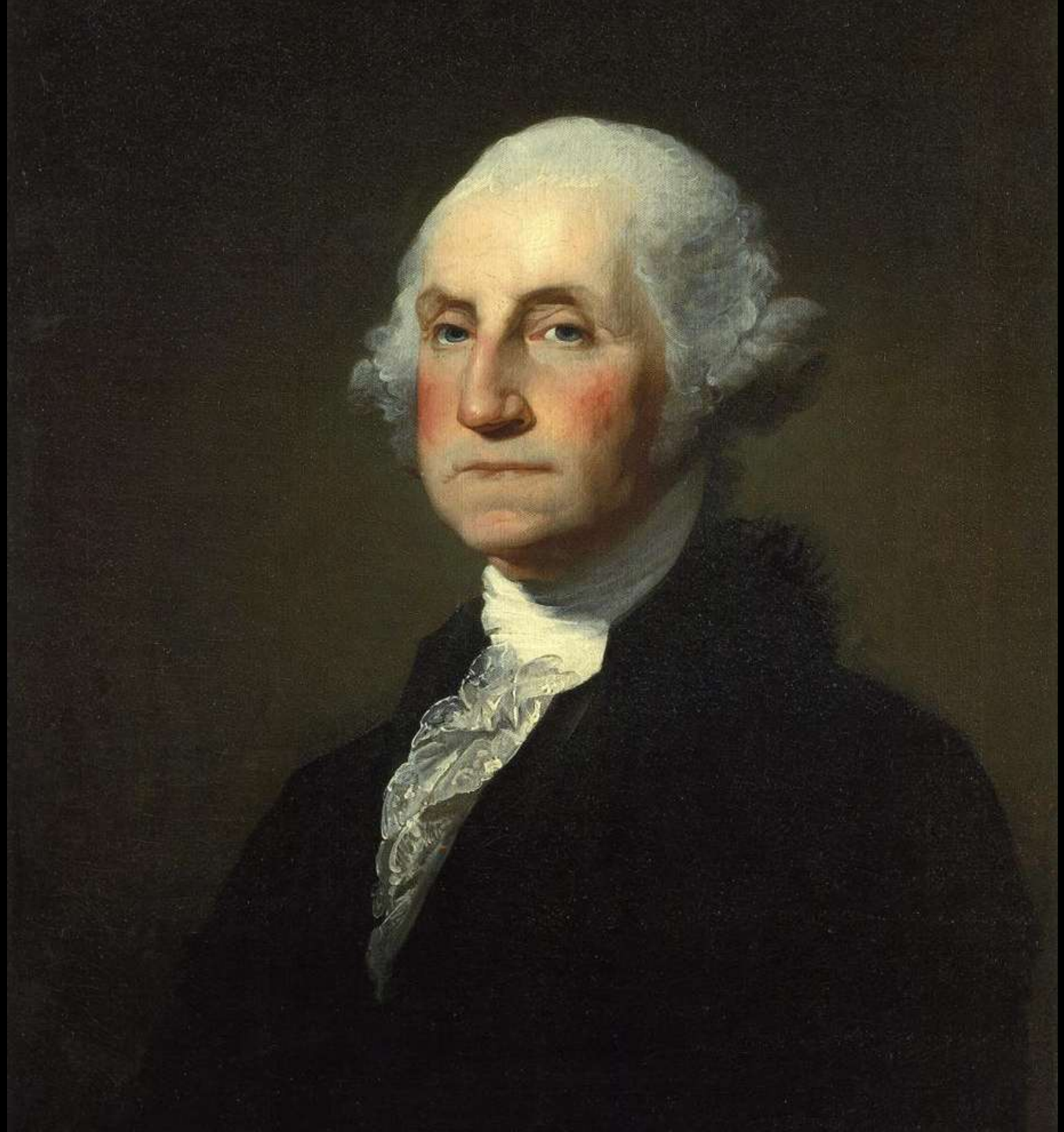
Clinical Reader in Epidemiology and Public Health

# This session's learning outcomes

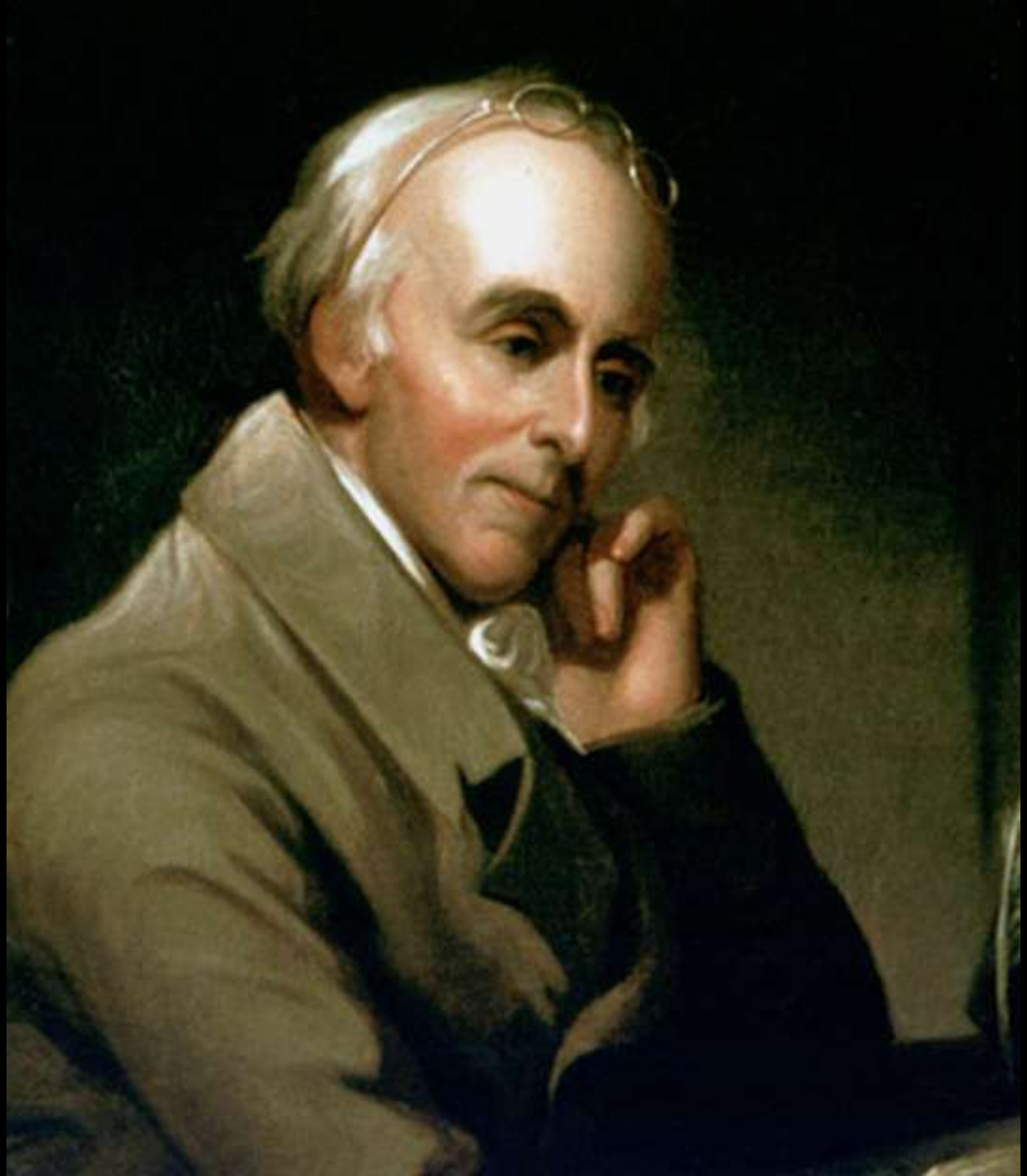
- Recognise the role of evidence based practice in clinical medicine
- List and define possible explanations for an observed associations (chance, bias, confounding, causation), and cite examples of each
- Be able to describe the hierarchy of evidence in study design
- List the Bradford-Hill criteria for establishing causation and apply these to specific examples
- Be able to apply epidemiological skills to clinical practice

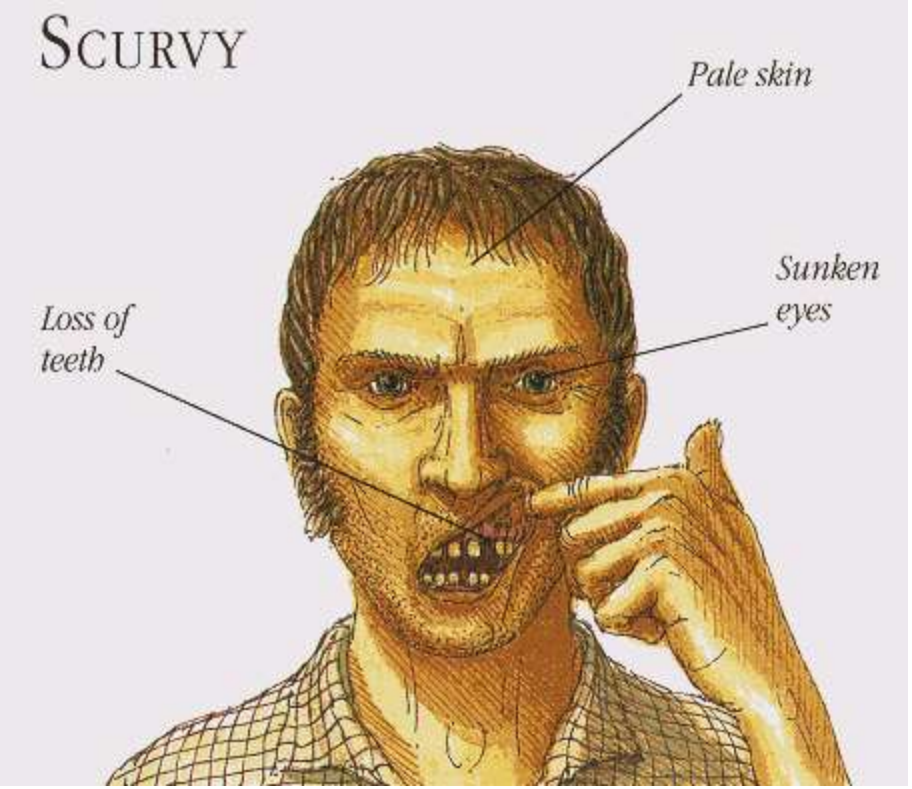


JAMES CRAIK,
PHYSICIAN GENERAL OF THE UNITED STATES ARMY

# 14th December 1799

- Albin Rawlins
  - Early hours 1/3 litre blood
- James Craik
  - Morning ½ litre blood
  - 11.00am ½ litre blood
  - Afternoon 1 litre blood
  - Appeared to recover slightly
  - Late evening – more blood-letting
    - Blood appeared viscous and didn't flow easily






- “Their gums were rotten even to the very roots of their very teeth, and their cheeks hard and swollen, the teeth were loose neere ready to fall out….. Their breath a filthy savour. The legs were feeble and so weak, that they were full of aches and paines, with many blewish and reddish staines or spots, some broad and some small like flea-biting.”
  - William Clowes, English Surgeon

# Alexander Hamilton 1809

- “It had been so arranged, that this number was admitted, alternately, in such a manner that each of us had one third of the whole. The sick were indiscriminately received, and were attended as nearly as possible with the same care and accommodated with the same comforts…..Neither Mr Anderson nor I ever once employed the lancet. He lost two, I four cases; whilst out of the other third, thirty-five patients died.”

# Evidence based medicine

- The concept of evidence based medicine has been evolving over the past 30 years.
- Methods to critically appraise clinical information and classify it according to the strength of evidence was first presented in a Canadian Medical Association Journal series on how to critically appraise literature in the early 1980's.

# Evidence based medicine

- Concepts emerging from the literature on “critical appraisal” promoted what has become known as evidence based medicine (EBM), suggesting that clinicians should use critically appraised information in clinical practice for optimal care of their patients

# Sackett defines Evidence Based Medicine as:

- The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients

BMJ 1996; 312: 71-72

# Criticism of EBM

- Attempts over the last 2 decades of the twentieth century to implement EBM in the UK and elsewhere generated a controversy that has questioned the value of EBM in clinical practice
- Some practicing doctors regard EBM as an academic exercise for medical students that has no relevance to clinical practice
- Often the translation of results from RCT'S conducted in teaching hospitals is not appropriate for General Practice

# Criticism of EBM

- It is impossible for any clinician to have the time to critically appraise even one article per week let alone the number that would need to be appraised to answer questions (estimated at 3.5 per clinical session) arising in a busy practice.
- Governments, healthcare commissioners and providers have used the jargon of EBM to justify decisions, directives, or incentives that are seen by clinicians as inappropriate

# Hierarchy of studies

- Systematic reviews and meta-analyses
- Randomised Controlled Trials
- Cohort studies
- Case-control studies
- Ecological studies
- Descriptive/cross-sectional studies
- Case report/series

# Resources

Cochrane Collaboration

- www.cochrane.org

Evidence-Based Medicine

- http://ebm.bmj.com/

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Area-wide traffic calming for preventing traffic related injuries **[Podcast]**
Antiviral treatment for Bell's palsy (idiopathic facial paralysis) **[Podcast]**
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Blood pressure lowering efficacy of diuretics as second-line therapy for primary hypertension **[Podcast]**
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As a clinician you are under constant pressure to have high-quality, up-to-date evidence at your fingertips. More

## For Researchers

The internet has given us instant access to a huge amount of research, but the large volume of available information is a problem in itself. More

## For Patients

Healthcare consumers and patients need high-quality evidence about the effectiveness of treatments. More

## For Policy Makers

As a policy maker or healthcare manager you are a generalist in search of high-quality information across a broad range of issues. More

# Evidence-Based MEDICINE for Primary Care and Internal Medicine

A digest of the very best new research of direct relevance to medical practice




**Current issue**

October 2009
Volume 14
Number 5

**Evidence-Based Medicine** surveys a wide range of international medical journals applying strict criteria for the quality and validity of research. Practising clinicians assess the clinical relevance of the best studies. The key details of these essential studies are presented in a succinct, informative abstract with an expert commentary on its clinical application.

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Therapeutics: Review: antenatal magnesium sulphate prevents cerebral palsy in preterm infants (30 Sep 2009)

Therapeutics: Review: combining 2 classes of blood pressure-lowering drugs has an approximately additive effect on systolic blood pressure (30 Sep 2009)

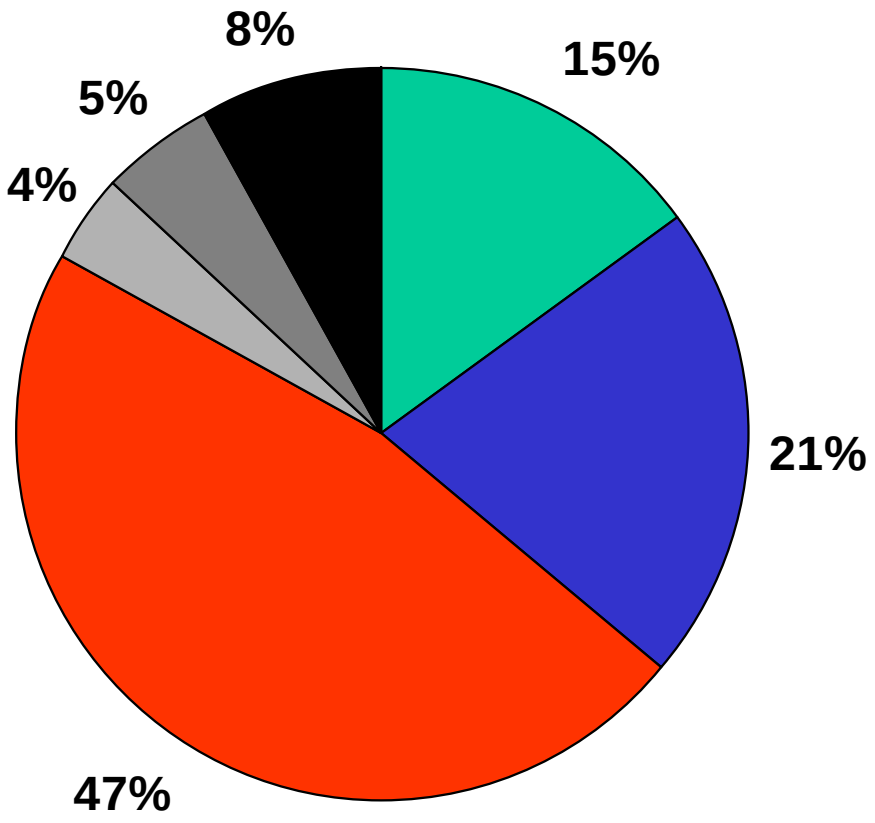
Therapeutics: Review: continuous positive airway pressure devices are effective and cost-effective for obstructive sleep apnoea (30



# Evidence based medicine

- Evidence based medicine does NOT replace clinical decision making but is only a tool

# How much do we know?



# Evidence based medicine

- **Clinical findings**
  - how to properly gather and interpret findings from the history and physical examination.
- **Aetiology**
  - how to identify causes for disease (including its iatrogenic forms).
- **Clinical manifestations of disease**
  - knowing how often and when a disease causes its clinical manifestations.
- **Differential diagnosis**
  - when considering the possible causes of a patient's clinical problem, how to select those that are likely, serious and responsive to treatment.

# Evidence based medicine

- **Diagnostic tests**
  - how to select and interpret diagnostic tests, in order to confirm or exclude a diagnosis, based on considering their precision, accuracy, acceptability, expense, safety, etc.
- **Prognosis**
  - how to estimate a  patient's likely clinical course over time and anticipate likely complications of the disorder.
- **Therapy**
  - how to select treatments to offer a patient that do more good than harm and that are worth the efforts and costs of using them.

# Evidence based medicine

- **Prevention**
  - how to reduce the chance of disease by identifying and modifying risk factors and how to diagnose disease early by screening.

# Homeopathy

## A systematic review of systematic reviews of homeopathy

**E. Ernst**

*Department of Complementary Medicine, School of Sport & Health Sciences, University of Exeter, 25 Victoria Park Road, Exeter EX2 4NT UK*

Homeopathy remains one of the most controversial subjects in therapeutics. This article is an attempt to clarify its effectiveness based on recent systematic reviews. Electronic databases were searched for systematic reviews/meta-analysis on the subject. Seventeen articles fulfilled the inclusion/exclusion criteria. Six of them related to re-analyses of one landmark meta-analysis. Collectively they implied that the overall positive result of this meta-analysis is not supported by a critical analysis of the data. Eleven independent systematic reviews were located. Collectively they failed to provide strong evidence in favour of homeopathy. In particular, there was no condition which responds convincingly better to homeopathic treatment than to placebo or other control interventions. Similarly, there was no homeopathic remedy that was demonstrated to yield clinical effects that are convincingly different from placebo. It is concluded that the best clinical evidence for homeopathy available to date does not warrant positive recommendations for its use in clinical practice.

*Keywords:* alternative medicine, clinical trials, homeopathy, meta-analysis, systematic review

### Introduction

Homeopathy is a therapeutic method using preparations of substances whose effects when administered to healthy subjects correspond to the manifestations of the disorder (symptoms, clinical signs, pathological states) in the individual patient. The method was developed by Samuel Hahnemann (1755–1843) and is now practised throughout the world [1]. Homeopathy is based on two main principals [1–3]. According to the 'like cures like' principle, patients with particular signs and symptoms can be helped by a homeopathic remedy that produces these signs and symptoms in healthy individuals. According to the second principle, homeopathic remedies retain biological activity after repeated dilution and sucussion even when diluted beyond Avogadro's number.

Few therapies have attracted more debate and controversy than homeopathy. Throughout its 200-year history, critics have pointed out that its very principles fly in the face of science, while proponents have maintained that it is narrow minded to reject an overtly helpful approach to healing only because one cannot explain how it might

rigorous trials that suggest efficacy, while critics had little trouble citing equally rigorous studies that implied the opposite.

The existence of contradicting evidence is not unusual in therapeutics. One solution to resolve such contradictions is to conduct systematic reviews and meta-analyses of rigorous studies. In 1997, Linde *et al.* [3] did just that. The conclusions of this technically superb meta-analysis expressed the notion that homeopathic medicines are more than mere placebos. The authors also stated that no indication was identified in which homeopathy is clearly superior to placebo. Despite this and other caveats, homeopaths worldwide celebrated this publication as the ultimate proof of their treatment. Since then, a flurry of interest in homeopathy has emerged, and several further systematic reviews have been published. This article is an attempt to critically evaluate all such papers published since 1997 with a view to defining the clinical effectiveness of homeopathic medicines.

### Methods

# Homeopathy

- "BMA estimates that the NHS spends about £4 million a year treating 54,000 patients in four homeopathic hospitals" [1]
- "Camden PCT spent £1.86m between 2005/8" [2]

[1] Telegraph http://www.telegraph.co.uk/health/alternativemedicine/7864217/Homeopathy-is-a-bitter-pill-for-the-taxpayer.html

[2] The Guardian http://www.guardian.co.uk/society/2009/jun/10/complementary-medicine-nhs-more4

# Where does epidemiology fit?

- Much of what underpins clinical medicine is epidemiological evidence

- “The study of the distribution of health related states or events and the determinants of health related states or events in specified populations, and the application of this study to control of health problems - to promote, protect and restore health”.

John Last

# Important problem

- In 1989 there were 1,340 sudden infant deaths
- Devastating for family

# "And this woman's child died in the night; because she overlaid it."

The first book of kings, old testament 500BC

# Theories Put Forward to Explain Sudden Infant Deaths

- Sudden arrest of breathing
- Infection
- Suffocation
- Inhalation of vomit
- Enlargement of the thymus (status thymico-lymphaticus)

# Status Thymo-lymphaticus

- Theory that enlarged thymus compresses the trachea and hinder respiration
- 1930s irradiation of the thymus gland in infancy recommended
  - The transactions of the second international paediatric congress, Stockholm, August 18-21, 1930. Acta Paediatr 1930;**11**:241-335

“After a most careful statistical investigation describe status thymo-lymphaticus as a good example of the growth of medical mythology, in which a nucleus of truth is buried beneath a pile of intellectual rubbish, conjecture, bad observations, and rash generalisation, and that it is as accurate to attribute the cause of death to ‘an act of god’ as to status lymphaticus”

William Boyd, A textbook of pathology 1963

# 1950s and 60s

- 1,400 infant deaths or 20% of the mortality of infants aged four weeks to two years in 1955
- Estimated rate in 1960 was 1.4 per 1000 live births

# Definition

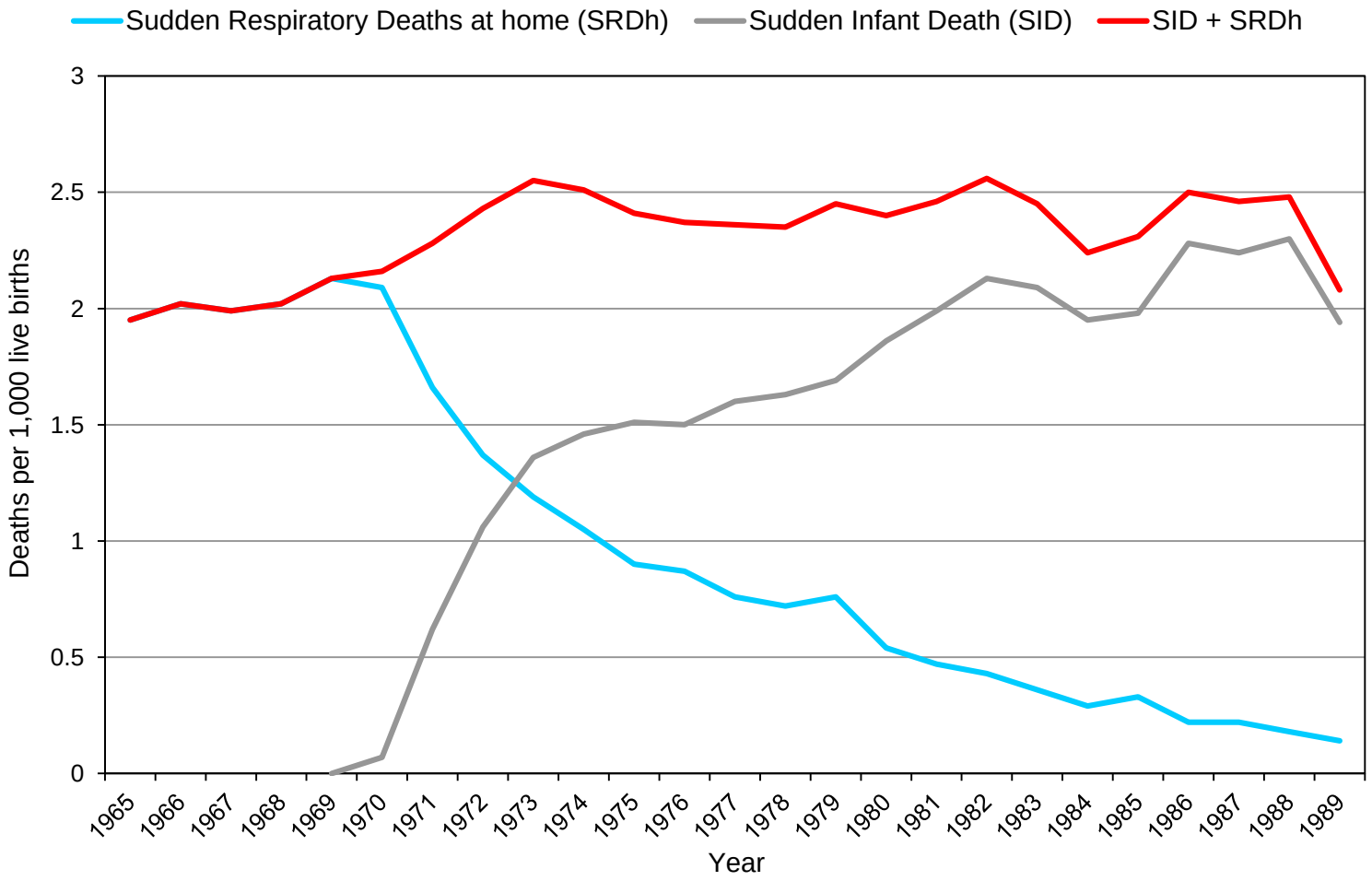
"The sudden death of any infant or young child which is unexpected by history, and in which a thorough post mortem examination fails to demonstrate an adequate cause for death".

– Beckwith J B (1970)

# 1970s

- Interest in sleeping position
- Fashion to place babies on front to avoid gastro-oesophageal reflux

# Cot death incidence (one week to one year) England and Wales 1965-1989



# Some proposed risk factors

- Toxic gas in mattresses
- Sleeping position
- Smoking
- Temperature/overwrapping
- Bottle feeding
- Infection
- Infanticide

# Case control studies

- Mitchell et al. Cot death supplement. Results from the first year of the New Zealand cot death study. *NZ Med J* 1991;**104**:71-76
- de Jonge et al. Cot death and prone sleeping position in the Netherlands. *BMJ* 1989;**298**:722
- Fleming et al. Interaction between bedding and sleeping position in the sudden infant death syndrome: a population-based case control study. *BMJ* 1990;**301**;85-9

# Fleming et al.

- All infants dying suddenly in Avon & Somerset over 18 month period
- Contacted GP and health visitor and asked to identify 2 other infants living in same neighbourhood of same age
- Parents visited ASAP as part of bereavement service - detailed structured interview

# Fleming et al.

- 67 unexplained deaths (cases)
- 134 comparison babies (controls)
- Detailed structured history
  - social factors
  - maternal medical history
  - pregnancy and perinatal history
  - medical history of baby
  - details of infants last sleep

# Odds ratio

| | Cases (Deaths) | Controls (comparison) |
|---|---|---|
| Exposed | a | b |
| Unexposed | c | d |
| Total | | |

$$\frac{\text{Odds of exposure in cases} = a/c}{\text{Odds of exposure in controls} = b/d}$$

# Sleeping position

| | Cases (Deaths) | Controls (comparison) |
|---|---|---|
| On front (Prone) | 62 | 76 |
| On side or back | 5 | 58 |
| Total | 67 | 134 |

# Sleeping position

| | Cases (Deaths) | Controls (comparison) |
|---|---|---|
| On front (Prone) | 62 | 76 |
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| Total | 67 | 134 |

Odds of lying on front in cases = 62/5 = 12.4

Odds of lying on front in controls = 76/58 = 1.3

OR = 12.4/1.3

= 9.5

# Environmental risk factors for SIDs

- Sleeping position (9x)
- Head covering (20x)
- Smoking in pregnancy 20 day (9x)

# REDUCE THE RISK OF COT DEATH

- Place your baby on the back to sleep
- Don't smoke and avoid smoky atmospheres
- Do not let your baby get too hot
- If you think your baby is unwell, contact your doctor

FSID





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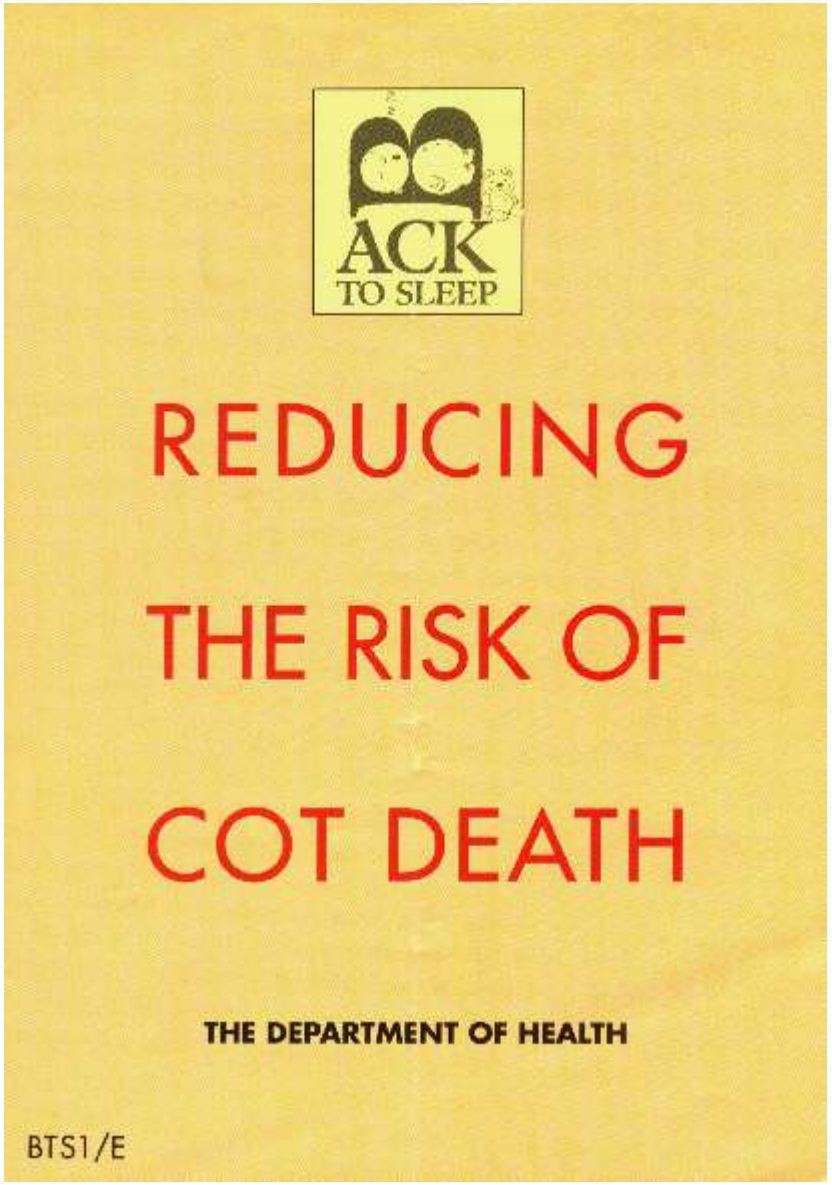

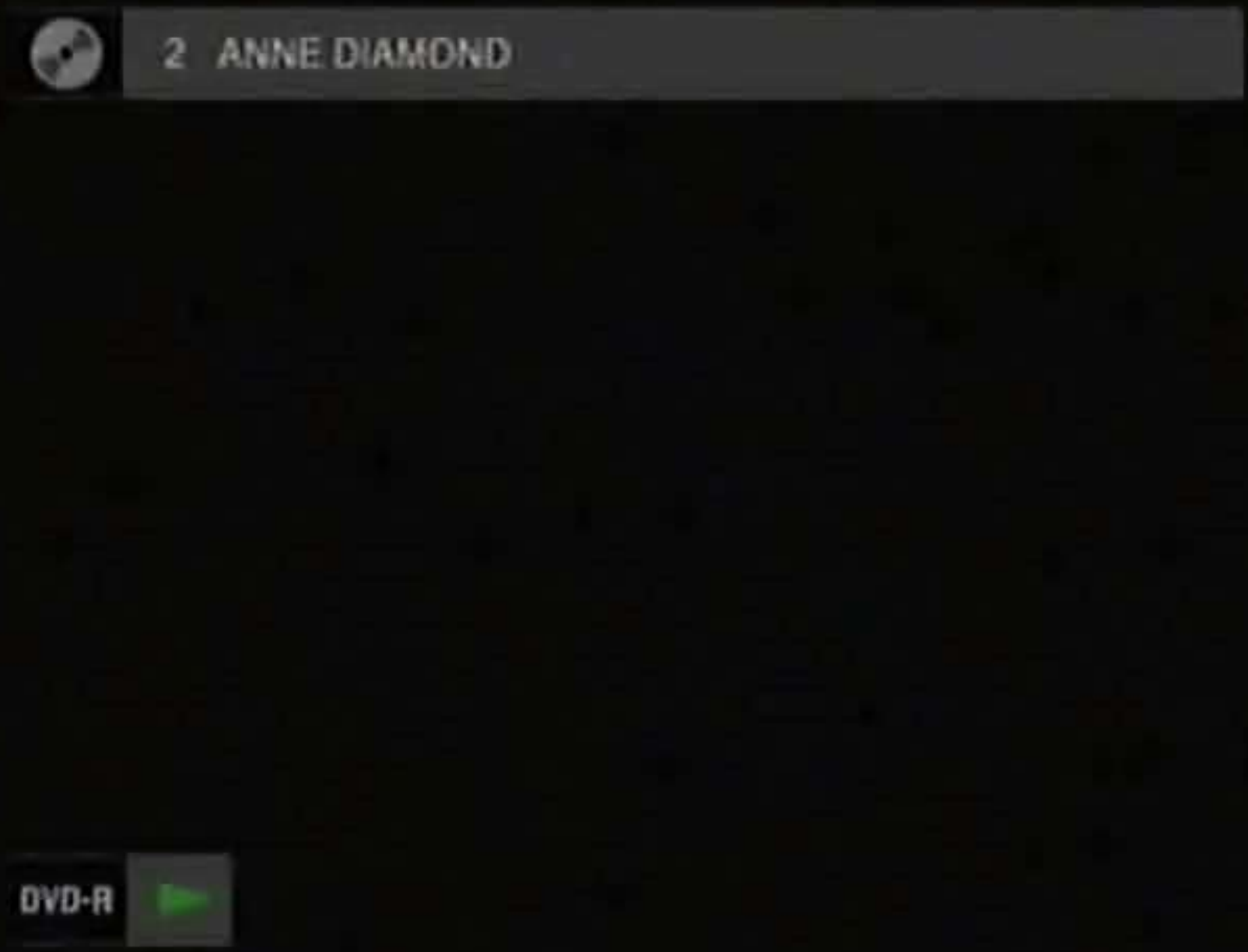
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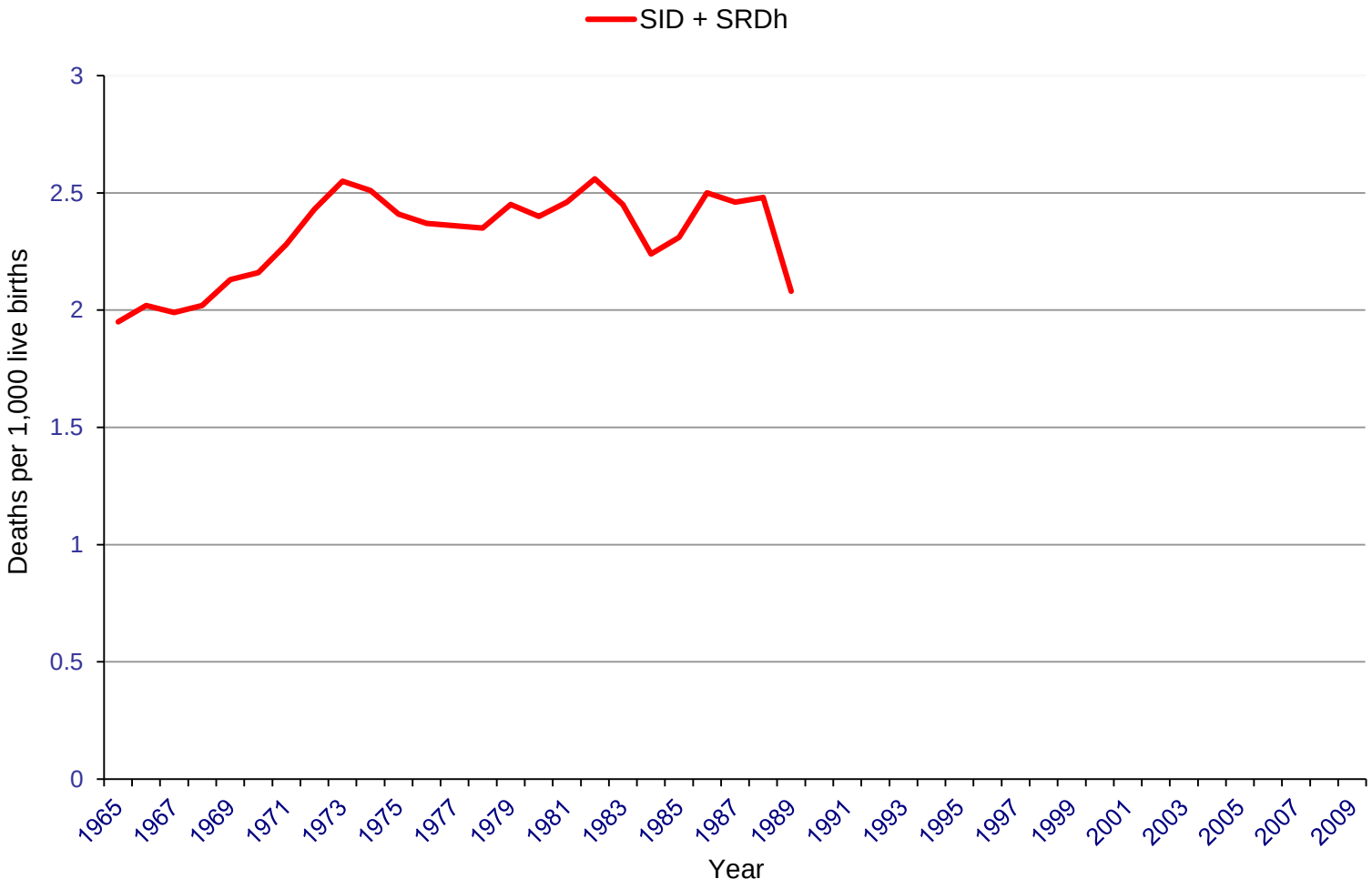
# Cot death incidence (aged 1 week to 1 year) England and Wales 1965-1989



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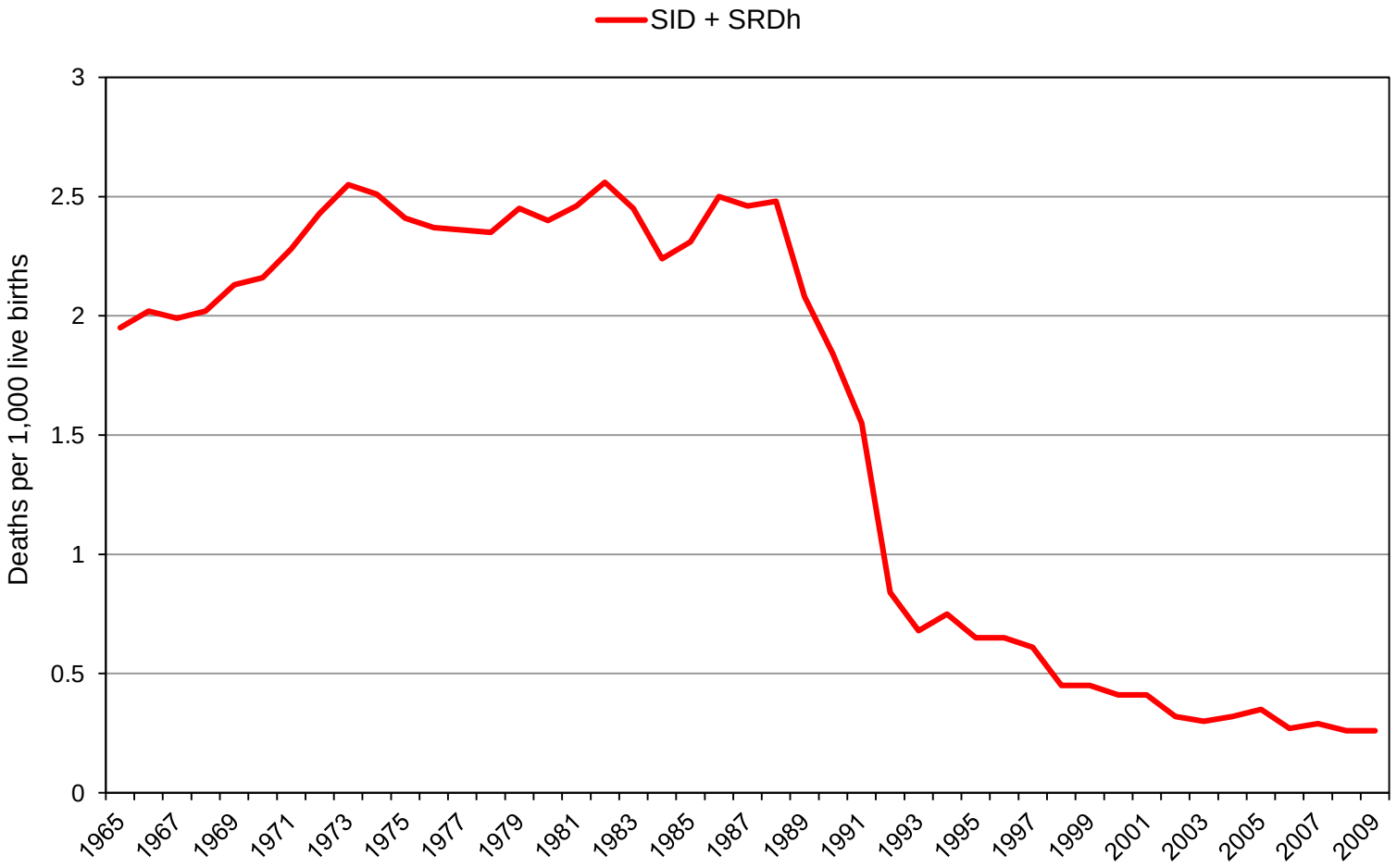
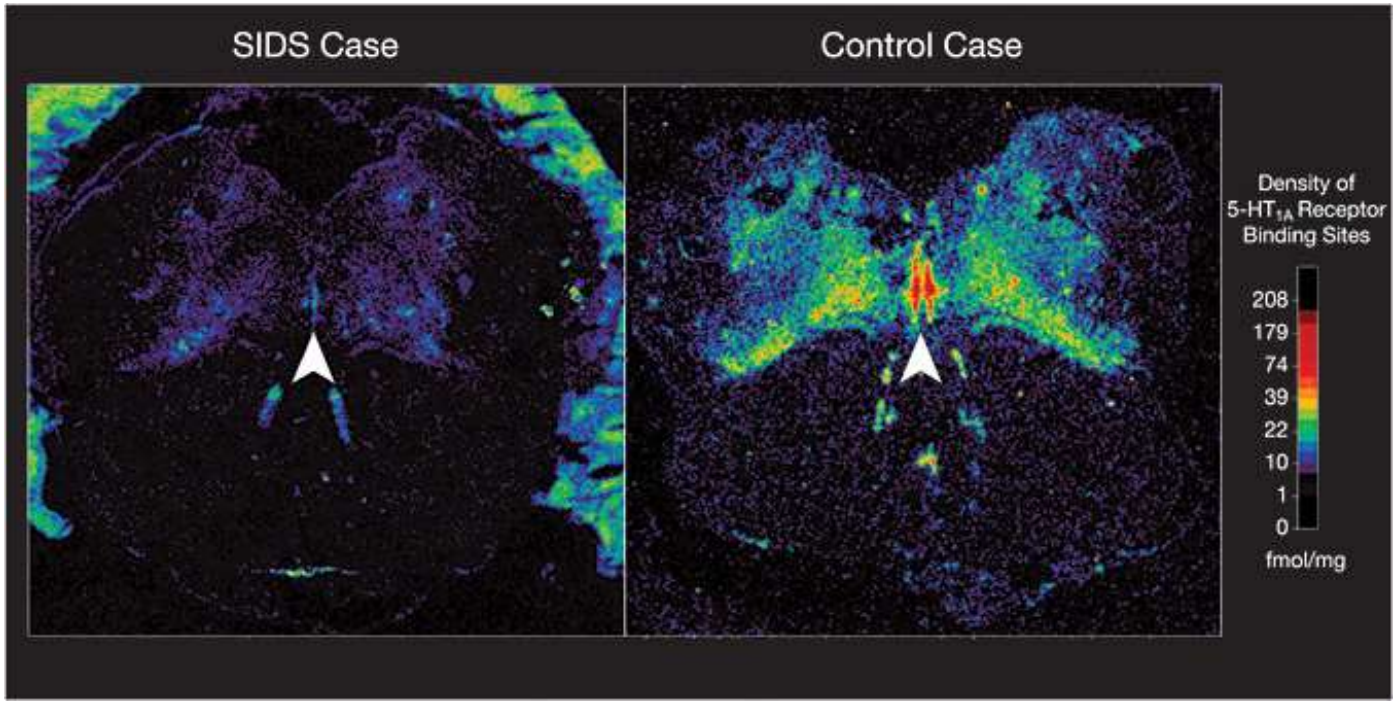


# SIDs in England and Wales

- Since 1991, the UK cot death rate has fallen by 75%, and has been hailed one of the most successful public health campaigns ever, estimated to have saved more than 15,000 lives.
- 1,326 deaths in 1989 down to 316 deaths in 2009*
- But cause still not known

* Office for National Statistics figures at fsid.org.uk

# 5-HT1A Receptor Binding Density in a SIDS Case and a Control




**Paterson, D. S. et al. JAMA 2006;296:2124-2132.**

# Multiple Serotonergic Brainstem Abnormalities in Sudden Infant Death Syndrome

David S. Paterson, PhD
Felicia L. Trachtenberg, PhD
Eric G. Thompson, MS
Richard A. Belliveau, BA
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Ryan Darnall, BA
Amy E. Chadwick, BA
Henry F. Krous, MD
Hannah C. Kinney, MD

**Context** The serotonergic (5-hydroxytryptamine [5-HT]) neurons in the medulla oblongata project extensively to autonomic and respiratory nuclei in the brainstem and spinal cord and help regulate homeostatic function. Previously, abnormalities in 5-HT receptor binding in the medullae of infants dying from sudden infant death syndrome (SIDS) were identified, suggesting that medullary 5-HT dysfunction may be responsible for a subset of SIDS cases.

**Objective** To investigate cellular defects associated with altered 5-HT receptor binding in the 5-HT pathways of the medulla in SIDS cases.

**Design, Setting, and Participants** Frozen medullae from infants dying from SIDS (cases) or from causes other than SIDS (controls) were obtained from the San Diego Medical Examiner's office between 1997 and 2005. Markers of 5-HT function were compared between SIDS cases and controls, adjusted for postconceptional age and postmortem interval. The number of samples available for each analysis ranged from 16 to 31 for SIDS cases and 6 to 10 for controls. An exploratory analysis of the correlation between markers and 6 recognized risk factors for SIDS was performed.

**Main Outcome Measures** 5-HT neuron count and density, 5-$HT_{1A}$ receptor binding density, and 5-HT transporter (5-HTT) binding density in the medullary 5-HT system; correlation between these markers and 6 recognized risk factors for SIDS.

**Results** Compared with controls, SIDS cases had a significantly higher 5-HT neuron count (mean [SD], 148.04 [51.96] vs 72.56 [52.36] cells, respectively; $P<.001$) and 5-HT neuron density ($P<.001$), as well as a significantly lower density of 5-$HT_{1A}$ receptor binding sites ($P\leq.01$ for all 9 nuclei) in regions of the medulla involved in homeostatic function. The ratio of 5-HTT binding density to 5-HT neuron count in the medulla was significantly lower in SIDS cases compared with controls (mean [SD], 0.70 [0.33] vs 1.93 [1.25] fmol/mg, respectively; $P=.001$). Male SIDS cases had significantly lower 5-$HT_{1A}$ binding density in the raphé obscurus compared with female cases (mean [SD], 16.2 [2.0] vs 29.6 [16.5] fmol/mg, respectively; $P=.04$) or with male and female controls combined (mean [SD], 53.9 [19.8] fmol/mg; $P=.005$). No association was found between 5-HT neuron count or density, 5-$HT_{1A}$ receptor binding density, or 5-HTT receptor binding density and other risk factors.

**Conclusions** Medullary 5-HT pathology in SIDS is more extensive than previously delineated, potentially including abnormal 5-HT neuron firing, synthesis, release, and clearance. This study also provides preliminary neurochemical evidence that may help explain the increased vulnerability of boys to SIDS.

*JAMA*. 2006;296:2124-2132 www.jama.com

SUDDEN INFANT DEATH SYNDROME (SIDS) is the leading cause of postneonatal infant mortality in the United States, with an overall incidence of 0.67/1000 live births.[1-3] Despite intensive research, the causes of SIDS remain unknown. Moreover, controversies abound about the role of certain practices, eg, bed sharing[4-5] or use of pacifiers,[5-7] in SIDS, in large part due to the lack of understanding of the basic biological mechanisms. We have proposed the triple risk model,[8] which suggests that sudden death results when 3 factors impinge on the infant simultaneously: (1) an underlying vulnerability; (2) an exogenous stressor (eg, prone sleep position, bed sharing); and (3) the critical developmental period, ie, the first 6 months of postnatal life, when the infant is at greatest risk for SIDS.[8]

The serotonergic (5-hydroxytryptamine [5-HT]) system of the medulla oblongata consists of 5-HT neurons located in the midline raphé, lateral extraraphé, and ventral surface and helps regulate autonomic and respiratory function.[1] These medullary nuclei are interconnected[9] and project extensively to nuclei in the brainstem and spinal cord that influence respiratory drive,[10] blood pressure regulation,[11] thermoregulation,[12] upper airway reflexes, and arousal.[13-15] Medullary 5-HT neurons have also been proposed to be central respiratory chemosensors.[16,17] Moreover, they are involved in the induction of long-term fa-

**For editorial comment see p 2143.**

Author Affiliations: Departments of Pathology (Drs Paterson and Kinney and Mssrs Thompson, Darnall, and Belliveau) and Pediatrics (Genetics) (Dr Beggs), Children's Hospital Boston and Harvard Medical School, Boston, Mass; New England Research Institutes, Watertown, Mass (Dr Trachtenberg); and Rady Children's Hospital and Health Center, San Diego, Calif, and University of California, San Diego School of Medicine (Ms Chadwick and Dr Krous).
Corresponding Author: David S. Paterson, PhD, 300 Longwood Ave, Enders Bldg Room 1109, Boston, MA 02115 (david.paterson@childrens.harvard.edu).

# Garlic pills and giving up smoking

- Four subjects who smoked were randomised into receiving garlic pills, a natural treatment, or a placebo to help them stop smoking. The two who received garlic pills stopped, the two who received placebo did not (p=0.33).
- **Conclusion** Garlic pill treatment facilitates giving up smoking

# Low mortality from heart disease in men who wear a silk tie

- A study was carried out to measure mortality from heart disease in men. A strong association was found between wearing a silk tie and low mortality.
- **Conclusion** Distribution of silk ties among the male population would reduce heart disease in the population

# Lecture feedback

- Using an online voluntary evaluation form, on a scale of 1 to 5, 90% of respondents rated the epidemiology undergraduate course a ‘5’ (excellent).

- **Conclusion** Epidemiology lectures are great

# Recent use of antacids and stomach cancer

- A study of people diagnosed with stomach cancer found cases had a much higher usage of antacids in the four months prior to diagnosis than matched controls
- **Conclusion** Usage of antacids is a cause of stomach cancer

# What is an association?

- Link
- Relationship
- Correlation

# What is an association

- Association refers to the statistical dependence between two variables, that is the degree to which the rate of disease in persons with a specific exposure is either higher or lower than the rate of disease without that exposure.

# Association and causation

- Chance
- Bias
- Confounding
- Cause

# Chance, coincidence

- Most studies based on an estimate from samples
- The role of chance can be assessed by performing appropriate **statistical significance** tests and by calculating **confidence intervals**

# Garlic pills and giving up smoking

- Four subjects who smoked were randomised into receiving garlic pills, a natural treatment, or a placebo to help them stop smoking. The two who received garlic pills stopped, the two who received placebo did not (p=0.33).
- **Conclusion** Results could be due to chance
- How would you get around chance in a study?

# Confidence intervals

- The range within which the ‘true’ value (e.g. the strength of an association) is expected to lie with a given degree of certainty (e.g. 95% or 99%)
- If independent samples are taken repeatedly from the same population, and a confidence interval calculated for each sample, then a certain percentage (e.g. 95%) of the intervals will include the true underlying population parameter

# P value

- The probability that a result could simply be due to chance

- Threshold usually <0.05 = 1/20
  - ie if p<0.05 we can be pretty sure (at least 95% certain) that result of a study is not due to chance
  - If p>0.05 then result could be due to chance

# Association and causation

- Chance
- Bias
- Confounding
- Cause

# Bias

- **Bias** is a systematic error leading to an incorrect estimate of the effect of an exposure on the development of a disease or **outcome** of interest. The observed effect will be either above or below the true value, depending on the nature of the systematic error.

# Bias

- **Bias** is a consequence of defects in the design or execution of an epidemiological study.
- **Bias** cannot be controlled in the analysis of a study, and it cannot be eliminated by increasing the sample size.

# Bias

Two broad types

- Selection
  - occurs when there is a systematic difference between the characteristics of the people selected for a study and the characteristics of those who were not.
- Measurement (or information)
  - occurs when measurements or classifications of disease or exposure are inaccurate

# Lecture feedback

- Using an online voluntary evaluation form, on a scale of 1 to 5, 90% of respondents rated the epidemiology undergraduate course a ‘5’ (excellent).
- 10 out of 380 students responded
- **Conclusion** Selection bias
- How would you get around bias in designing a study?

# Association and causation

- Chance
- Bias
- Confounding
- Cause

# Confounding

- A potential confounder is any factor which is believed to have a real effect on the risk of the disease under investigation and is also related to the risk factor under investigation.
- This includes
  - factors that have a direct causal link with the disease (e.g. smoking and lung cancer)
  - factors that are good proxy measures of more direct unknown causes (e.g. age and social class).

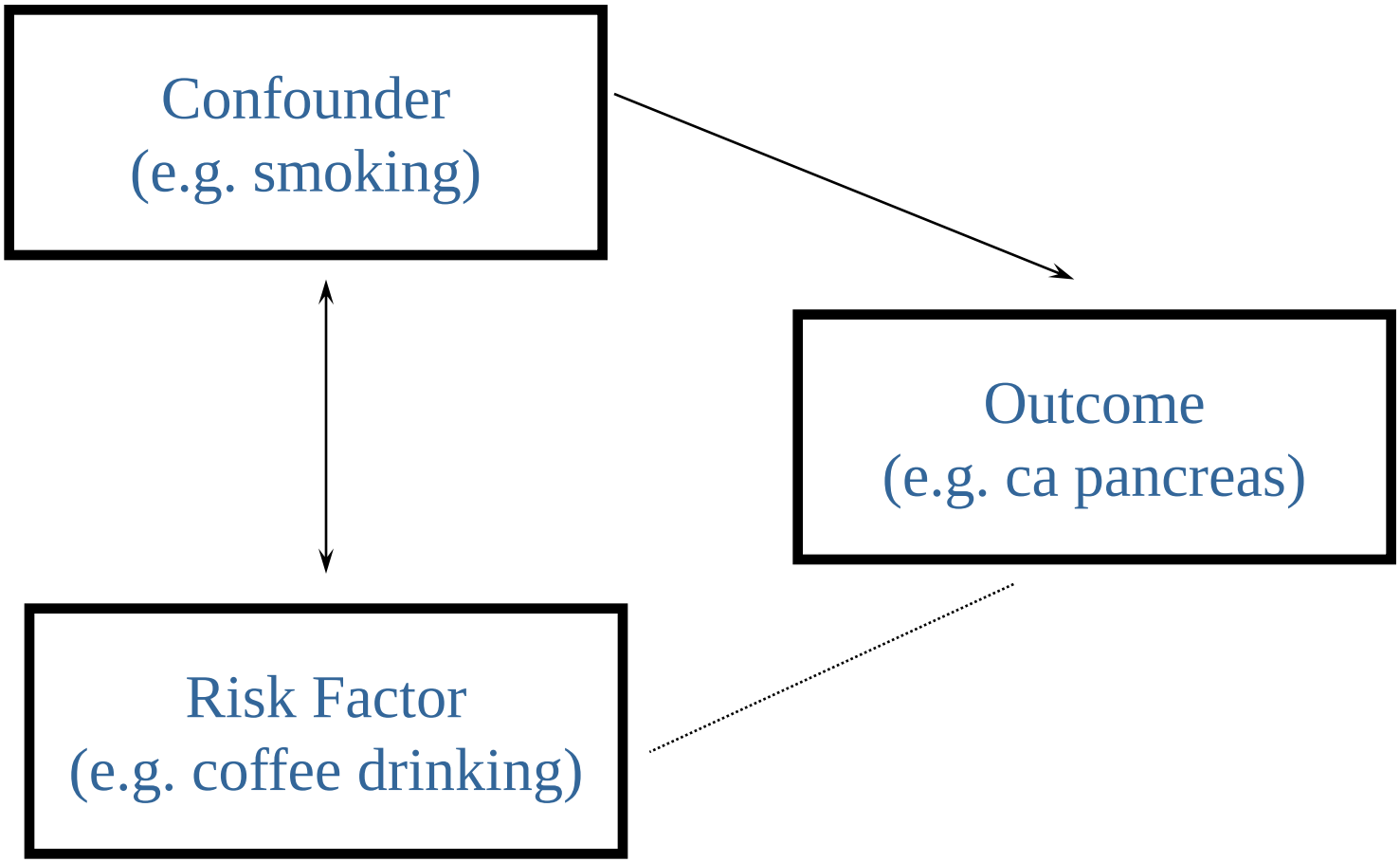
# Common confounders

- Age
- Sex
- Socio-economic status
  - Poorer people have rates of almost all diseases
- Geography
  - Disease prevalence varies greatly by place
  - North and South

# Confounding - example

- Coffee consumption is associated with the risk of cancer of the pancreas.
- Disputed because coffee consumption is correlated with cigarette smoking, and cigarette smoking was known to be a risk factor for pancreatic cancer.

# Confounding



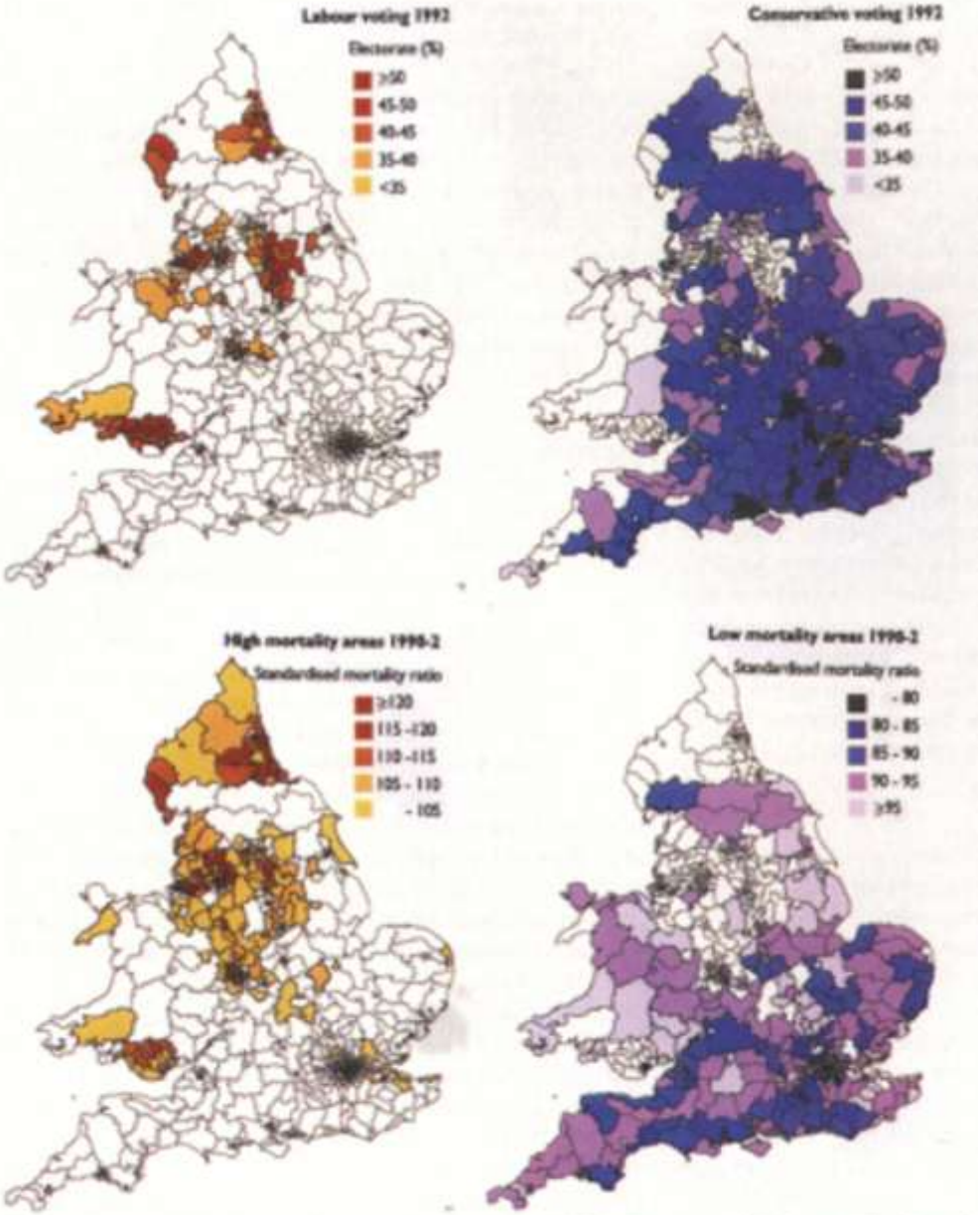



**Fig 1**—*Maps of Labour and Conservative voting in 1992 with maps of high mortality (standardised mortality ratio in white areas <100) and low mortality areas in 1990-2 (standardised mortality ratio in white areas >100)*

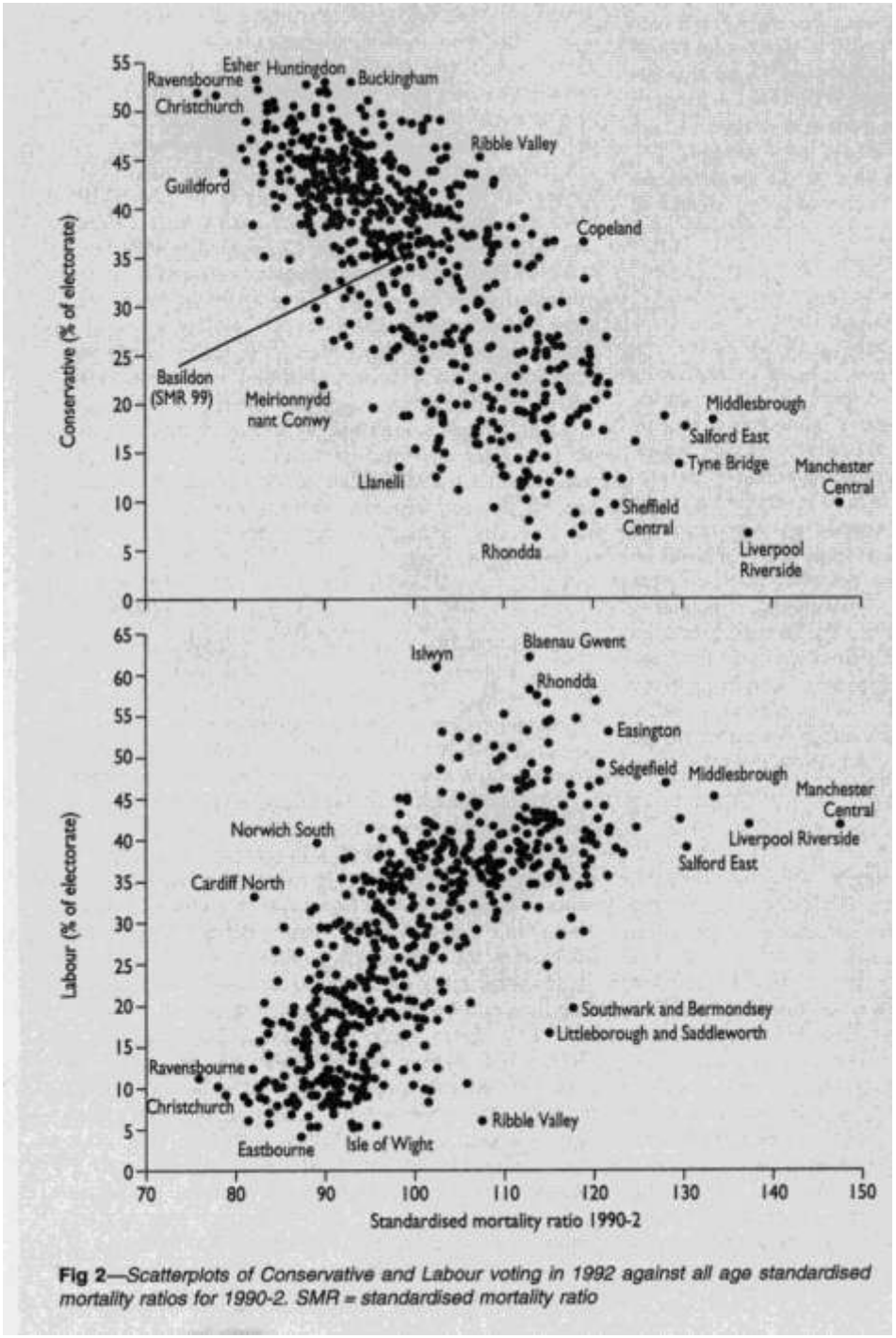



**Fig 2**—*Scatterplots of Conservative and Labour voting in 1992 against all age standardised mortality ratios for 1990-2. SMR = standardised mortality ratio*

# Low mortality from heart disease in men who wear a silk tie

- A study was carried out to measure the mortality from heart disease in men. A strong association was found between wearing a silk tie and low mortality.
- **Conclusion** Social class is a confounder

- How would you get around confounding in a study?

# Association and causation

- Chance
- Bias
- Confounding
- Cause

# Causation

- Judgement based on a chain of logic that addresses two main areas:
  - Observed association between an exposure and a disease is valid
  - Totality of evidence taken from a number of sources supports a judgement of causality

# Causation - Bradford Hill 1965

*Factors to consider*

- Temporal relationship
- Plausibility
- Consistency with other investigations
- Strength of the association
- Dose-response relationship
- Specificity
- Experimental evidence
- Coherence
- Analogy

*also consider reversibility*

# Recent use of antacids and stomach cancer

- A study of people diagnosed with stomach cancer found cases had a much higher usage of antacids in the four months prior to diagnosis than matched controls
- **Conclusion** Stomach cancer is likely to precede usage of antacids - reverse causation

# Causation - Bradford Hill 1965

*Factors to consider*

- Temporal relationship
- Plausibility
- Consistency with other investigations
- Strength of the association
- Dose-response relationship
- Specificity
- Experimental evidence
- Coherence
- Analogy

*also consider reversibility*

# Association and causation

- Bias
- Chance
- Confounding
- Cause

# Break

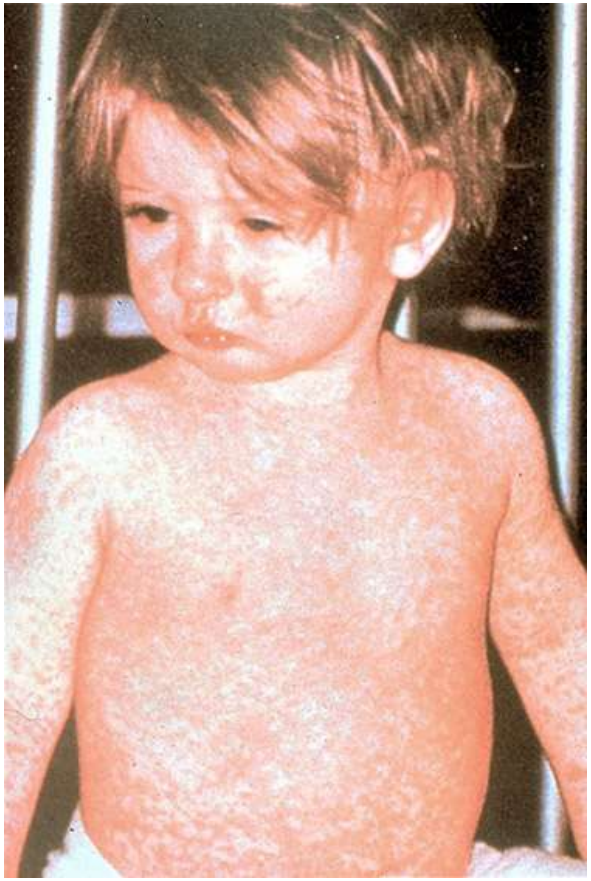
# MMR

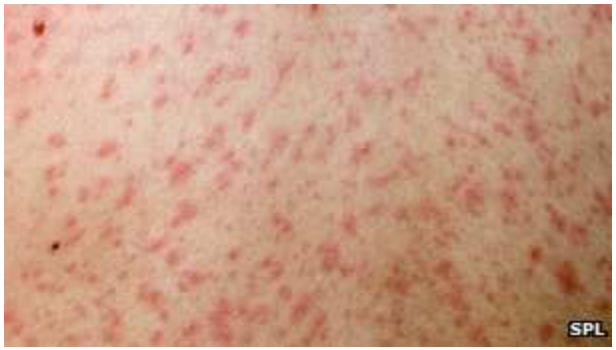
- Combined vaccine
  - measles, mumps and rubella (German measles)
- Given in two stages, at ages 12-15 months and 3-5 years.
- Since MMR was introduced in the UK in 1988 the number of children catching these diseases has fallen to an all-time low

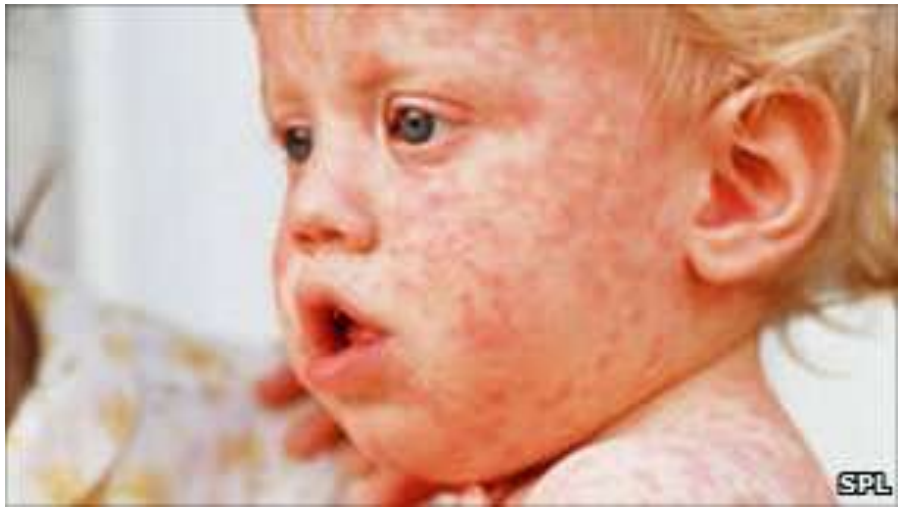
# Why is it given?

- Measles vaccine prevents deaths and complications from measles, a potentially serious viral illness
- The mumps vaccine prevents mumps, which was the biggest cause of viral Meningitis in children
- The rubella vaccine prevents babies being damaged if their mother catches rubella when pregnant

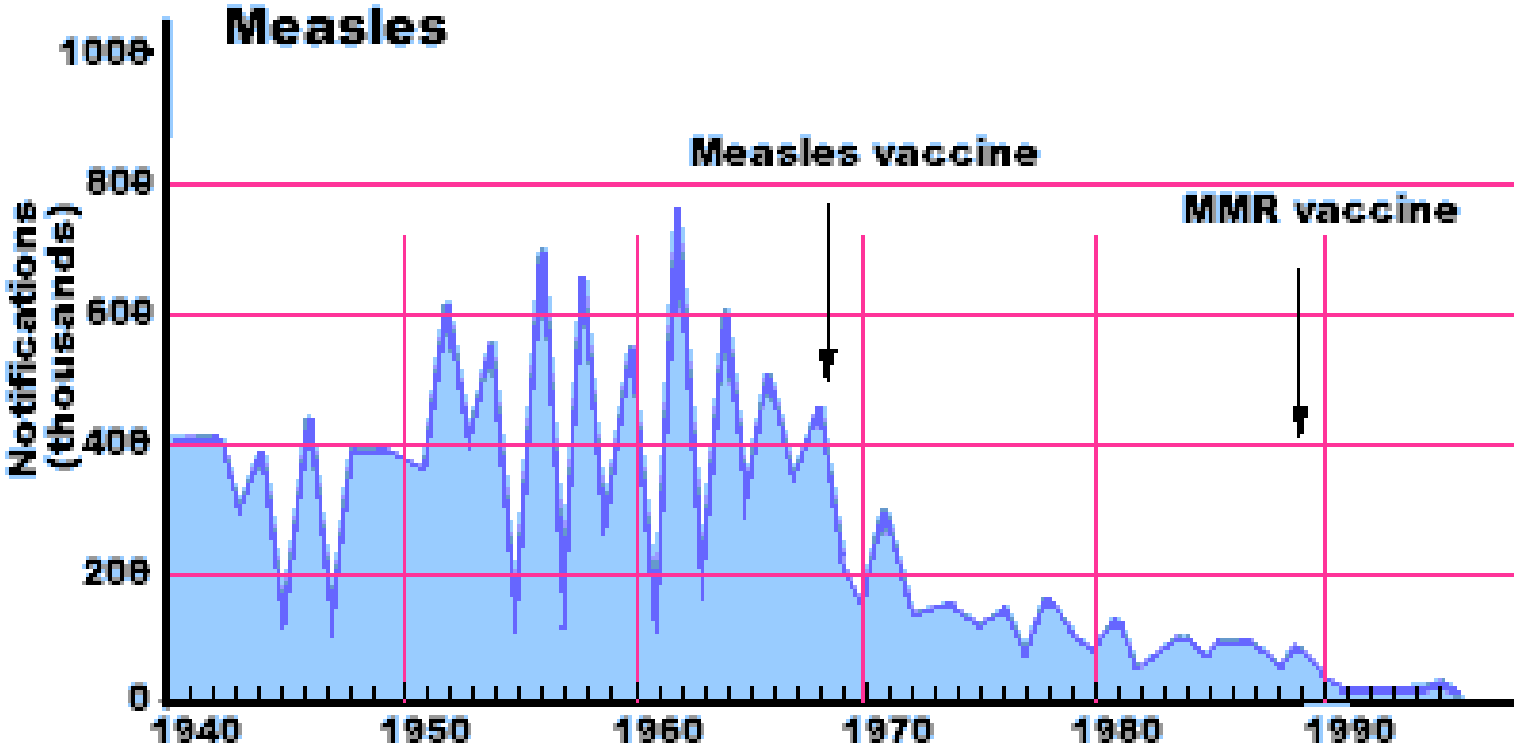
# Measles



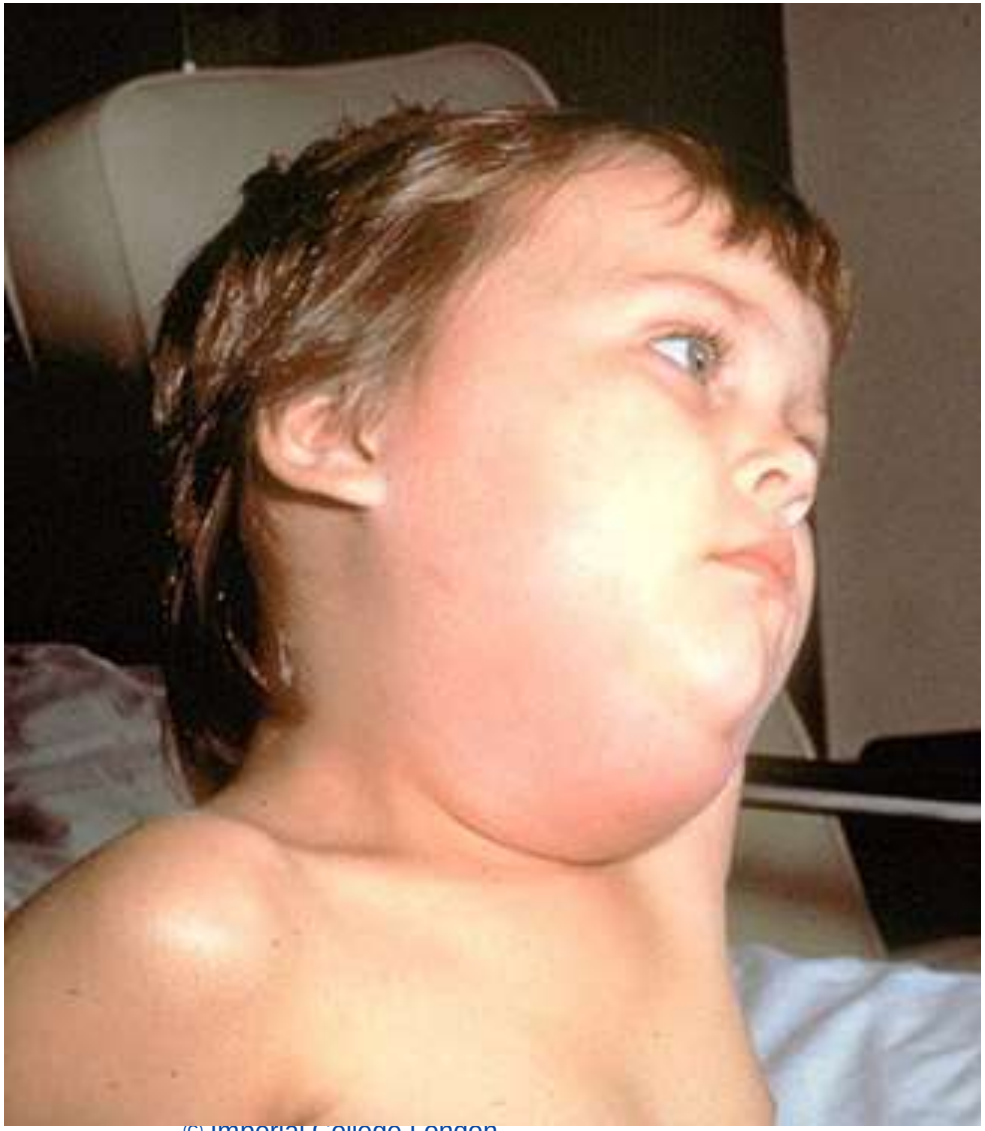


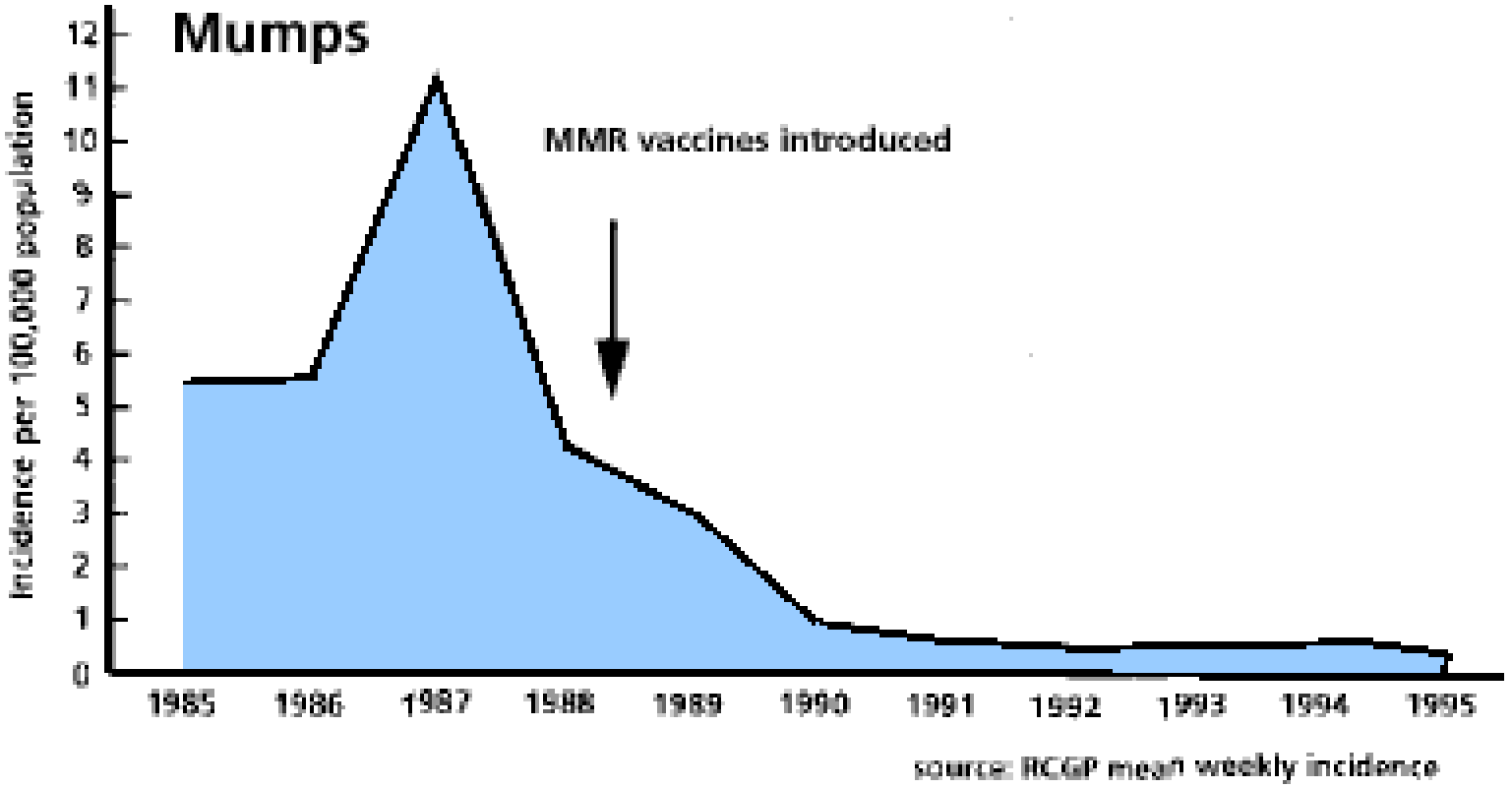
# Measles



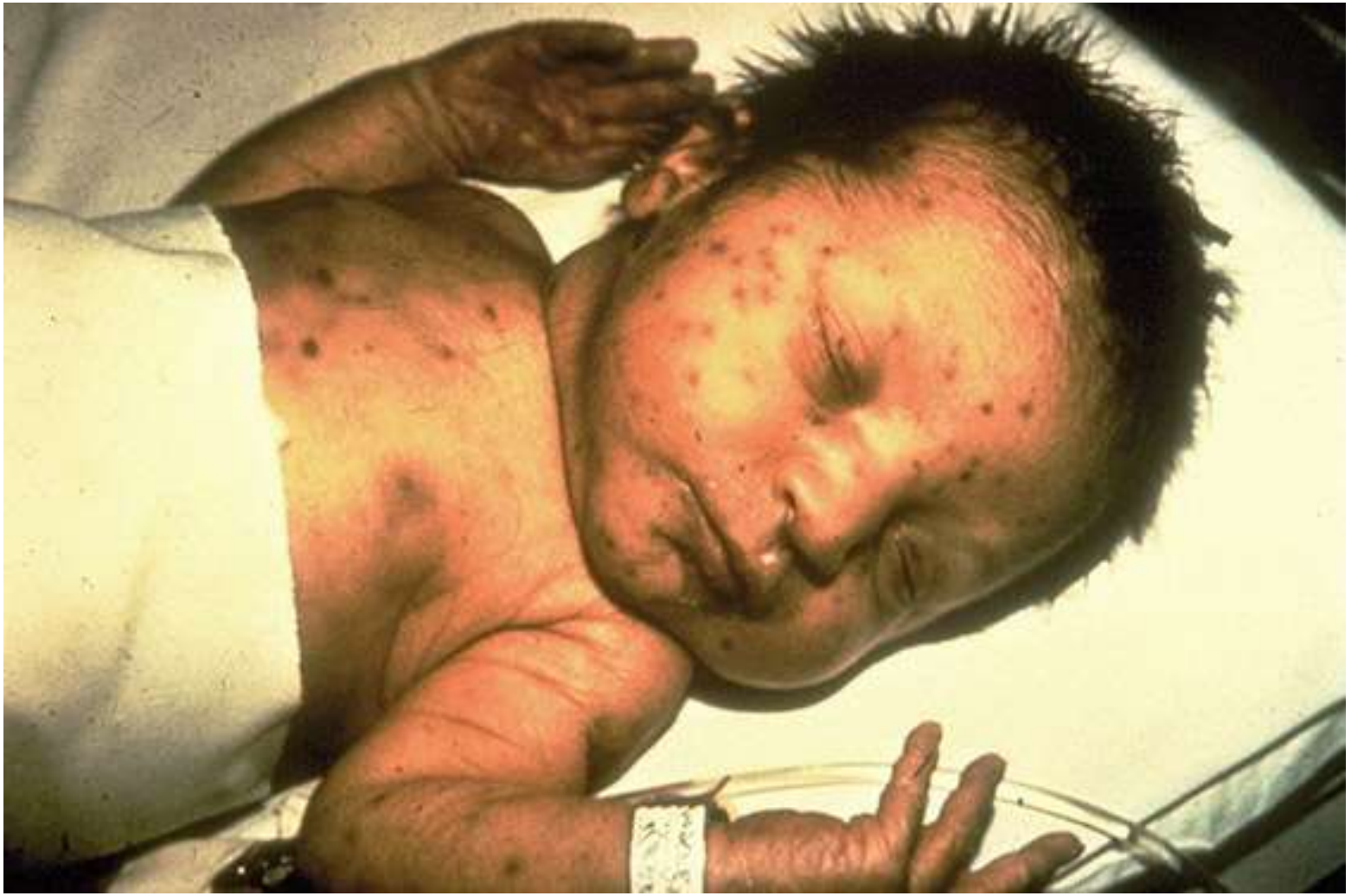
# Mumps



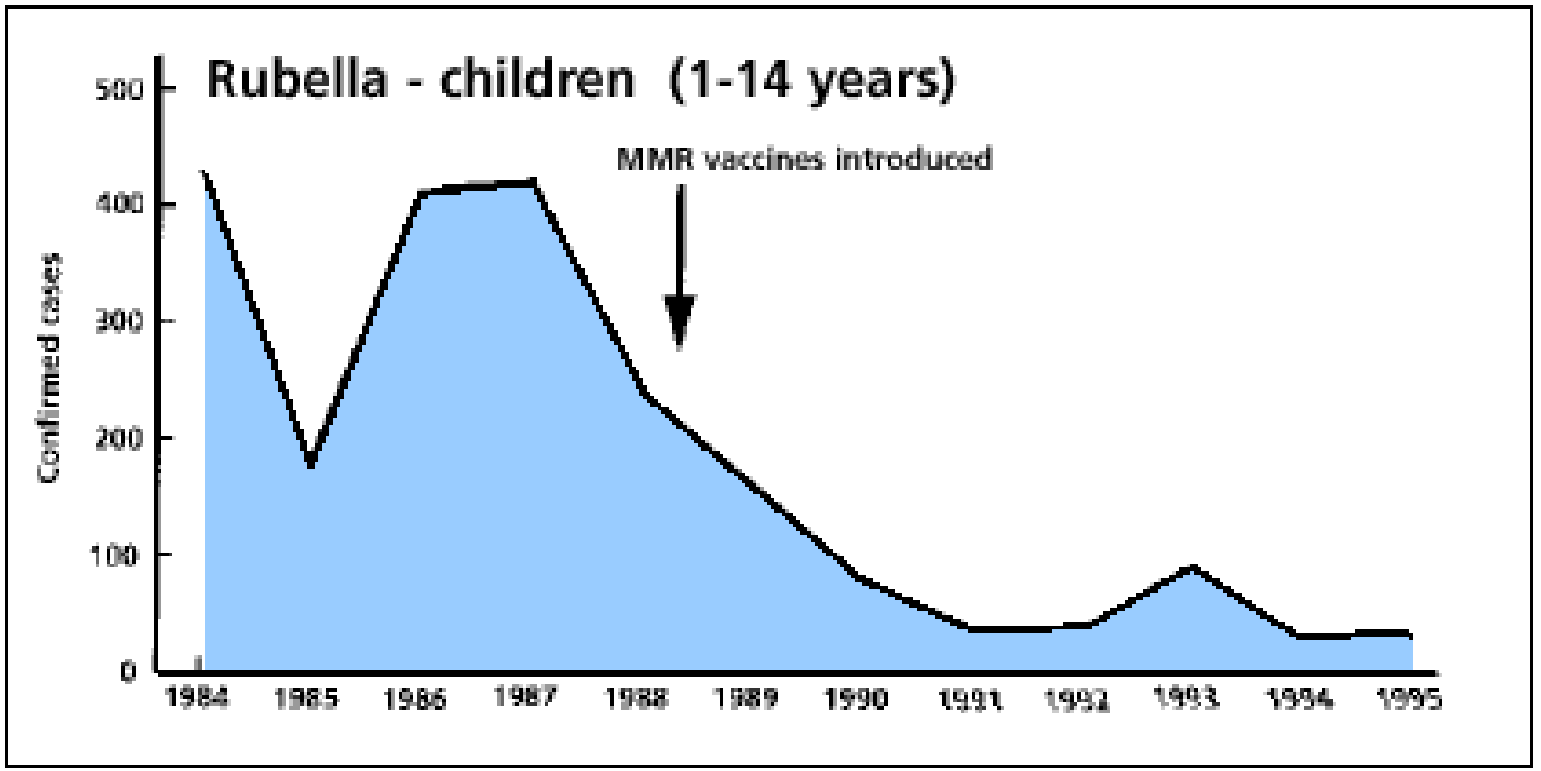
# Mumps



# Rubella



# Rubella




- Rubella infection is not shown for young men, in whom it is higher, because they have not been immunised routinely

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. 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, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12

## 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 bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

## Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

### *Clinical investigations*

We took histories, including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental histories included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all

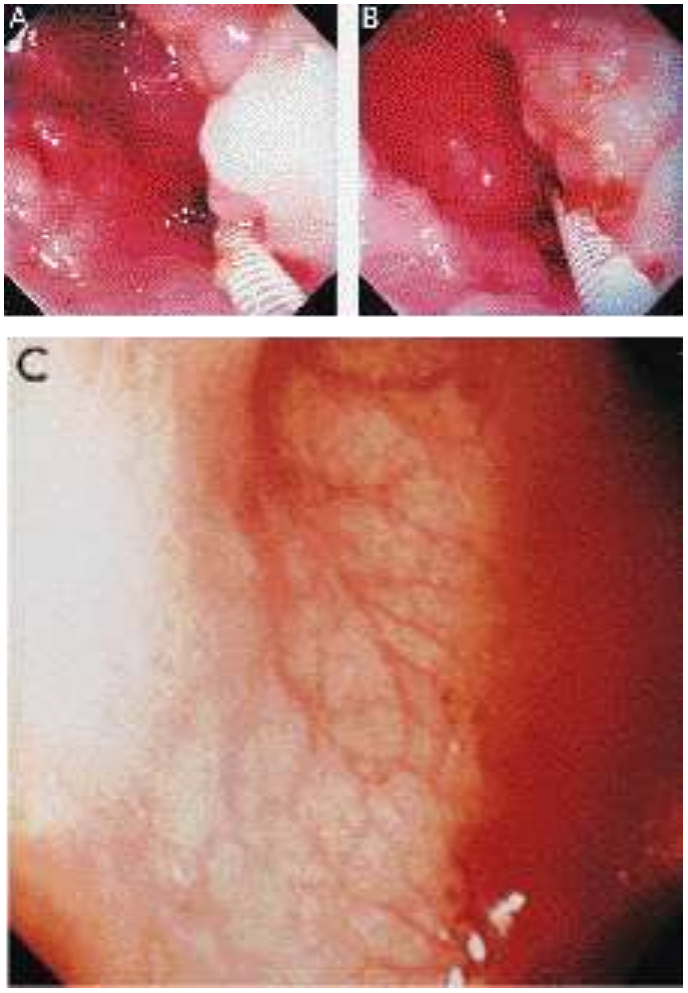
# Abstract

- Investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.
- 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.

# Investigations

- Children underwent a number of gastroenterological, neurological, and developmental assessment and review of developmental records
  - Ileocolonoscopy and biopsy sampling
  - magnetic-resonance imaging (MRI)
  - electroencephalography (EEG)
  - lumbar puncture
  - Barium follow-through radiography was done where possible
  - Biochemical, haematological, and immunological profiles

# Endoscopic view of terminal ileum in child three and in a child with endoscopically and histologically normal ileum and colon



# Findings

- Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children
- With measles infection in one child, and otitis media in another.
- All 12 children had intestinal abnormalities
- Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two)

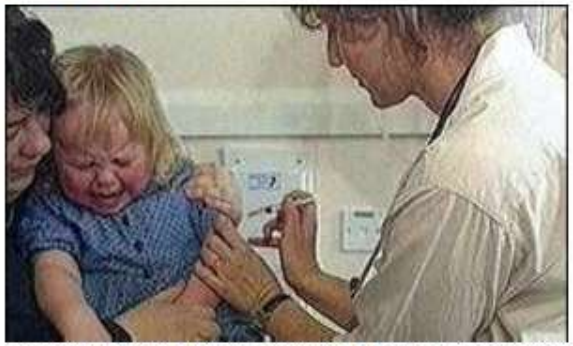
# Conclusions of authors

- “We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers”

# Possible explanations

UK

# Child vaccine linked to autism



Research says some children's behaviour changed after vaccine given

A study by doctors at the Royal Free Hospital in London has suggested that a common childhood vaccine may be linked with autism and cause an intestinal disorder.

The BBC's health correspondent Fergus Walsh reports (0'58")

The research has discovered a new inflammatory bowel disease which is associated with autistic children.

Dr Andrew Wakefield: "overload" fears

The head of the research team, Dr Andrew Wakefield, raised alarms because children's behaviour changed drastically shortly after they received the controversial single dose of the measles, mumps and rubella vaccine.

He believes that the combination of the three virus strains may overload the body's immune system and cause the bowel

jabs
Justice Awareness and Basic Support

# Welcome to the support group for vaccine-damaged children

Single Jab Clinics

News
Vaccine News & Info
Because of the volume of visitors to jabs.org.uk, we've had to move our news coverage... just click here for our Vaccine news and Information

Discussion forums:
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About vaccines
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## Doctor blames ministers for loss of faith in MMR

London Evening Standard
15 January 2003

A LEADING paediatrician has accused the Government of losing the trust of parents over the MMR vaccine.

Dr David Elliman said ministers had "gone over the top" in using heavy-handed tactics to persuade people to accept the controversial three-in-one jab.

He said parents had so little faith in the measles, mumps and rubella vaccine that it would now be "very difficult" to regain public trust in it.

Dr Elliman is the local immunisation co-ordinator for south London and in the past has regularly been wheeled out by the Government to defend MMR.

While he supports the vaccine and says the alternative of single jabs should not be offered on the NHS, Dr Elliman criticised the way the Government has promoted its use. Speaking at a Science Museum debate on MMR, he said: "People have lost trust in the Government over MMR."

"The Government has gone over the top in the way it has gone about persuading people of its safety. Its tactics have been heavy-handed and people have been put off. The other problem is that scandals such as BSE mean that when the Government says something is safe, people simply do not believe them."

He added: "It is now very difficult to see how you can persuade parents that MMR is safe. It has got to be down to doctors, rather than the glossy pamphlets."

International version | About th

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## Mumps epider

**Doctors say they a a mumps epidemi 10-fold increase i suspected cases and Wales comp last year.**

There have bee suspected case the Health Pro the first four year, compar

More than t and 24, wh

Experts ar are prote

Mumps i is trans droplet sneeze

It is s close pers kiss

Th

U immunisation

WATCH LIVE BBC News 24

Last Updated: Wednesday, 14 November 2007,

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## Measles outbreaks hits 30

**Almost 300 children in east London have been diagnosed with measles in the past five months, figures show.**

City and Hackney Primary Care Trust (CHPCT) reported 297 cases since June compared with their yearly average of between 10 and 20 cases.

The number of children receiving t after research - since discredited MMR and autism.

CHPCT is now using a mobile unit among children.

### Unfortunate episode

Nine years ago a paper by Dr A with autism was published in t

According to experts, despite evidence of a link, this was o decline in immunisations.

Dr Mike Fitzpatrick, said: "It episode where an unsubsta a major impact on a nation

"So much so that a signifi withdrawn their children f have a return of diseases

In response to this a spe

Mea

Dr Paul Cleary, of the HPA, said: "Measles and mumps are very infectious and can cause serious complications. Children and young adults are more prone to the diseases, the HPA said.

### MMR vaccine

Most measles cases in recent years have occurred among children aged under five.

In the North West, Greater Manchester has reported the largest number of measles and mumps cases so far this year.

Dr Cleary urged parents to make sure their children have been given the vaccine against the two illnesses.

He said: "Children and young adults can be safely and effectively protected from measles and mumps by receiving two doses of the MMR vaccine.

"Unfortunately many children have not had this, are now seeing more children affected by

So far this year, Greater M confirmed cases of 196, and Cumb

Gre

BC NEWS CHANNEL

Page last updated at 14:17 GMT, Wednesday, 12 August 2009 15:17 UK

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## Fears over measles and mumps rise

**The number of measles and mumps cases has risen dramatically across the north west of England, according to the Health Protection Agency (HPA).**

In the first half of 2009 there were 481 mumps cases, compared to 164 during the same period last year.

The number of measles cases more than doubled during the same period, rising from 44 to 92.


The MMR jab protects against measles, mumps and rubella

Imperial College London

# Hierarchy of studies

- Systematic reviews and meta-analyses
- Randomised Controlled Trials
- Cohort studies
- Case-control studies
- Ecological studies
- Descriptive/cross-sectional studies
- Case report/series

# Association and causation

- Chance
- Bias
- Confounding
- Cause

# Causation - Bradford Hill 1965

*Factors to consider*

- Temporal relationship
- Plausibility
- Consistency with other investigations
- Strength of the association
- Dose-response relationship
- Specificity
- Experimental evidence
- Coherence
- Analogy

*also consider reversibility*

[Intervention Review]

# Vaccines for measles, mumps and rubella in children

Vittorio Demicheli[1], Tom Jefferson[2], Alessandro Rivetti[3], Deirdre Price[4]

[1]Health Councillorship - Servizio Regionale di Riferimento per l'Epidemiologia, SSEpi-SeREMI - Cochrane Vaccines Field, Regione Piemonte - Azienda Sanitaria Locale ASL AL, Torino, Italy. [2]Vaccines Field, The Cochrane Collaboration, Roma, Italy. [3]Servizio Regionale di Riferimento per l'Epidemiologia, SSEpi-SeREMI - Cochrane Vaccines Field, Azienda Sanitaria Locale ASL AL, Alessandria, Italy. [4]Department of Clinical Pharmacology, University of Oxford, Oxford, UK

Contact address: Vittorio Demicheli, Health Councillorship - Servizio Regionale di Riferimento per l'Epidemiologia, SSEpi-SeREMI - Cochrane Vaccines Field, Regione Piemonte - Azienda Sanitaria Locale ASL AL, C.so Regina Margherita 153 bis, Torino, Piemonte, 10122, Italy. Vittorio.DeMicheli@regione.piemonte.it. vittorio.demicheli@regione.piemonte.it. (Editorial group: Cochrane Acute Respiratory Infections Group.)

*Cochrane Database of Systematic Reviews*, Issue 4, 2008 (Status in this issue: *Edited, commented*)

DOI: 10.1002/14651858.CD004407.pub2
This version first published online: 19 October 2005 in Issue 4, 2005. Re-published online with edits: 8 October 2008 in Issue 4, 2008. Last assessed as up-to-date: 18 December 2004. (Dates and statuses?)

This record should be cited as: Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD004407. DOI: 10.1002/14651858.CD004407.pub2.

Next >

## Abstract

### Background
Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness.

### Objectives
We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR.

### Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2004, Issue 4), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used.

# The studies included in the review were as follows:

- five randomised controlled trials (RCTs)
- one controlled clinical trial (CCT)
- fourteen cohort studies
- five case-control studies
- three time-series trials
- one case-crossover trial
- one ecological trial
- one self-controlled case series trial

# Authors' conclusions

- "Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR)."

# Causation - Bradford Hill 1965

*Factors to consider*

- Temporal relationship
- Plausibility
- Consistency with other investigations
- Strength of the association
- Dose-response relationship
- Specificity
- Experimental evidence
- Coherence
- Analogy

*also consider reversibility*

# Retraction of an interpretation

This statement refers to the Early Report "Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children",[1] published in *The Lancet* in 1998. It is made by 10 of the 12 original authors who could be contacted. It should be noted that this statement does not necessarily reflect the views of the other co-authors.

The main thrust of this paper[1] was the first description of an unexpected intestinal lesion in the children reported. Further evidence has been forthcoming in studies from the Royal Free Centre for Paediatric Gastroenterology and other groups to support and extend these findings.[2,3] While much uncertainty remains about the nature of these changes, we believe it important that such work continues, as autistic children can potentially be helped by recognition and treatment of gastrointestinal problems.

We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient. However, the possibility of such a link was raised and consequent events have had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed upon these findings in the paper, according to precedent.[4]

We were unable to contact John Linnell.

*Simon H Murch, Andrew Anthony, David H Casson, Mohsin Malik, Mark Berelowitz, Amar P Dhillon, Michael A Thomson, Alan Valentine, Susan E Davies, John A Walker-Smith

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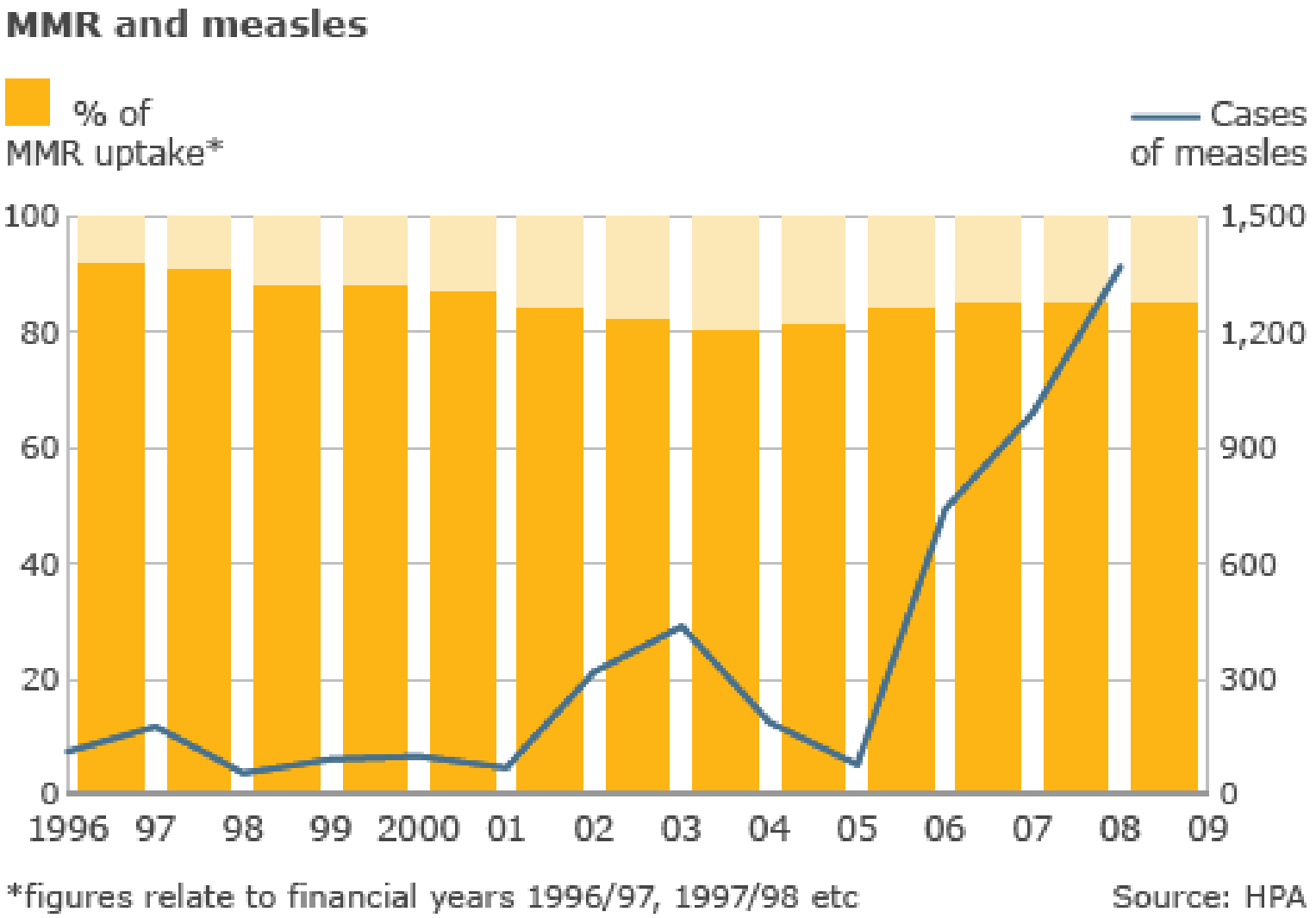
(e-mail: s.murch@rfc.ucl.ac.uk)

1 Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowtiz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.

2 Murch S. MMR and autism: the debate continues. *Lancet* 2004; 363: 568–69.

3 Horvath K, Perman JA. Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr* 2002; 14: 583–87.

4 Zhang L, Lopez P, He T, Yu W, Ho DD. Retraction of an interpretation. *Science* 2004; 303: 467.




http://news.bbc.co.uk/1/hi/8695267.stm

17 February 2012 Last updated at 17:36



# MMR jab urged after measles cases at Ysgol Eifionydd, Porthmadog

**Parents are being urged to get their children vaccinated with the MMR jab after an increase in measles cases at a school in Gwynedd.**

Parents are being urged to get their children vaccinated

Ten children associated with Ysgol Eifionydd secondary school in Porthmadog have been diagnosed so far.

All cases had either had no MMR vaccination, or only one dose - two doses are needed.

A vaccination session for children who have not had both doses will take place at the school on 22 February.

Parents at the school in Porthmadog will receive a letter on Monday about the outbreak.

Dr Chris Whiteside, consultant in communicable disease control for Public Health Wales said many of the cases under investigation had not received their scheduled MMR vaccinations.

"Measles is highly contagious and spreads very easily. We would therefore expect to see more

Related Stories

Measles outbreak vaccination call

MMR vaccine uptake 'rises to 90%'

# This session's learning outcomes

- Recognise the role of evidence based practice in clinical medicine
- List and define possible explanations for an observed associations (chance, bias, confounding, causation), and cite examples of each
- Be able to describe the hierarchy of evidence in study design
- List the Bradford-Hill criteria for establishing causation and apply these to specific examples
- Be able to apply epidemiological skills to clinical practice

# Further reading