

The importance of evidence in the practice of medicine

8th March 2013

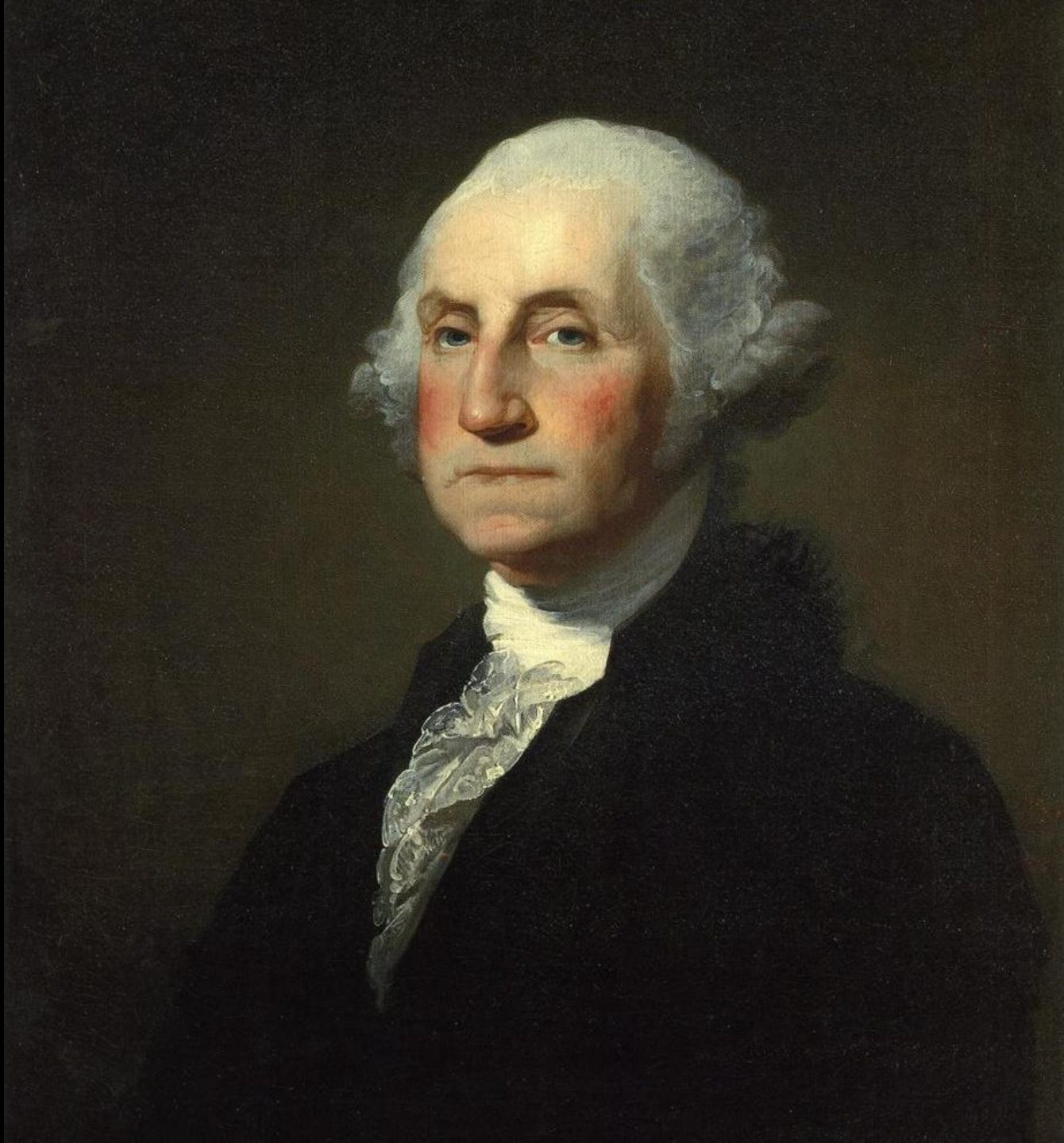
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Clinical Reader in Epidemiology and Public Health

Quiz



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 decision making





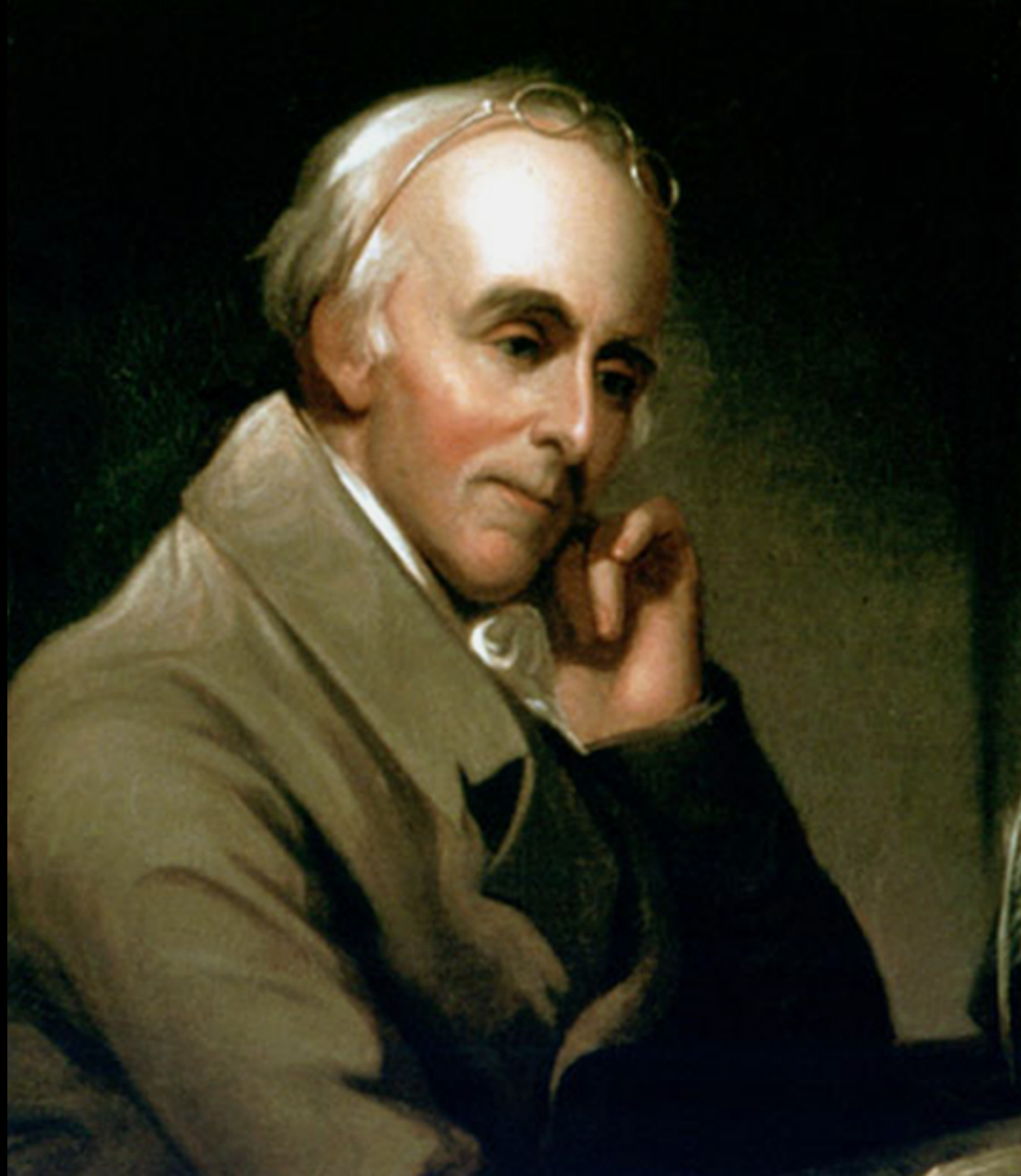


JAMES CRAIK,
PHYSICIAN GENERAL OF THE UNITED STATES ARMY

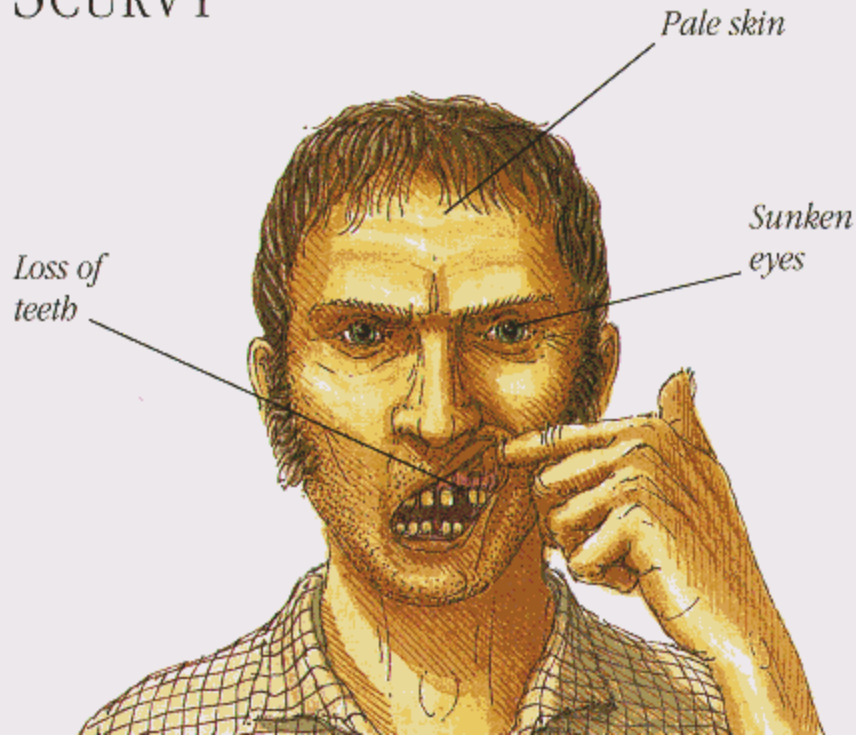
14th December 1799

- Albin Rawlins
 - Early hours 1/3 litre blood
- James Craik
 - Morning 1/2 litre blood
 - 11.00am 1/2 litre blood
 - Afternoon 1 litre blood
 - Appeared to recover slightly
 - Late evening – more blood-letting
 - Blood appeared viscous and didn't flow easily





SCURVY



- “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.”

- But many doctors slated the evidence.... particularly the so-called “numerical method”..... they were more interested in treating the individual patient lying in front of them, than in what might happen to large numbers.

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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EDITORIAL

General health checks in adults for reducing morbidity and mortality from disease



Since the latter half of the 20th century, technological advances in modern medicine and a growing emphasis on preventive care have led to increased enthusiasm for screening in apparently healthy people. In primary care practice, the general health check (also termed periodic health evaluation or routine medical examination) is the usual mechanism used to screen asymptomatic people for disease. Although widely practiced, there is no universally accepted definition of what constitutes a general health...

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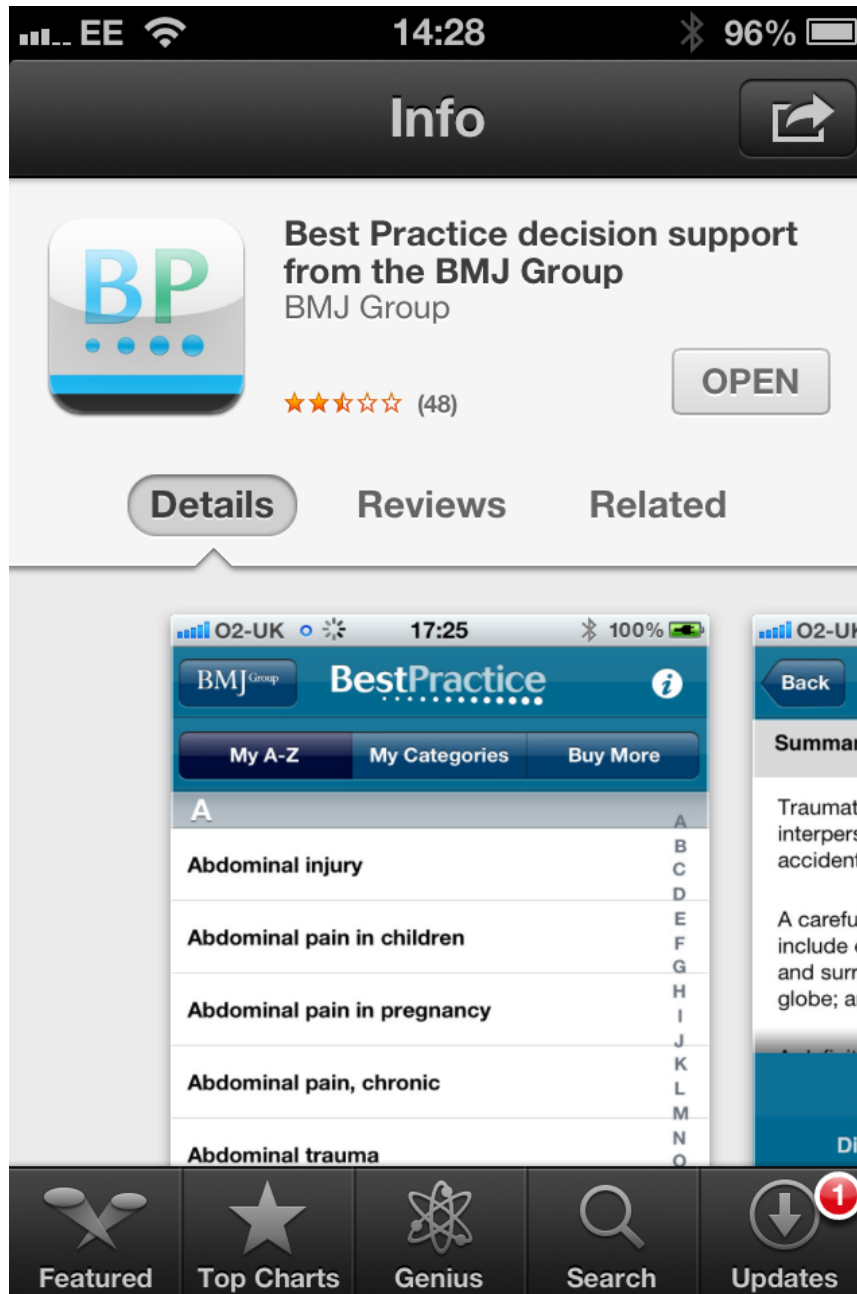
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Why EBM Should Matter to Clinicians

- Revalidation
- Patient Care
- Medical Knowledge
- Professionalism

Evidence based medicine

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

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

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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 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 principles [1–3]. Homeopathy is based on 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 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 work [2]. Similarly, proponents have quoted seemingly

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 homeopathy was identified in which homeopathy is clearly superior to placebo. Despite this and other caveats, homeopathy worldwide celebrated this publication as the ultimate proof of their treatment. Since then, a flurry of systematic reviews have been published, and several further interest in homeopathy has emerged, and several further attempt to critically evaluate all such papers published since 1997 with a view to defining the clinical effectiveness of homeopathic medicines.

Methods

Literature searches were carried out in the following databases: Medline (via Pubmed), Embase, Amed, CISCOM (from inception to October 2001). The search terms used were homeopathy homeopathy clinical trial, meta-analysis, systematic review, efficacy, effectiveness. In addition, other experts in the field

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>

4 October 2012 Last updated at 01:43



Should the NHS pay for homeopathy?

By Steven Brocklehurst

BBC Scotland news website



Homeopathy uses very diluted substances which are given orally, often on a pill

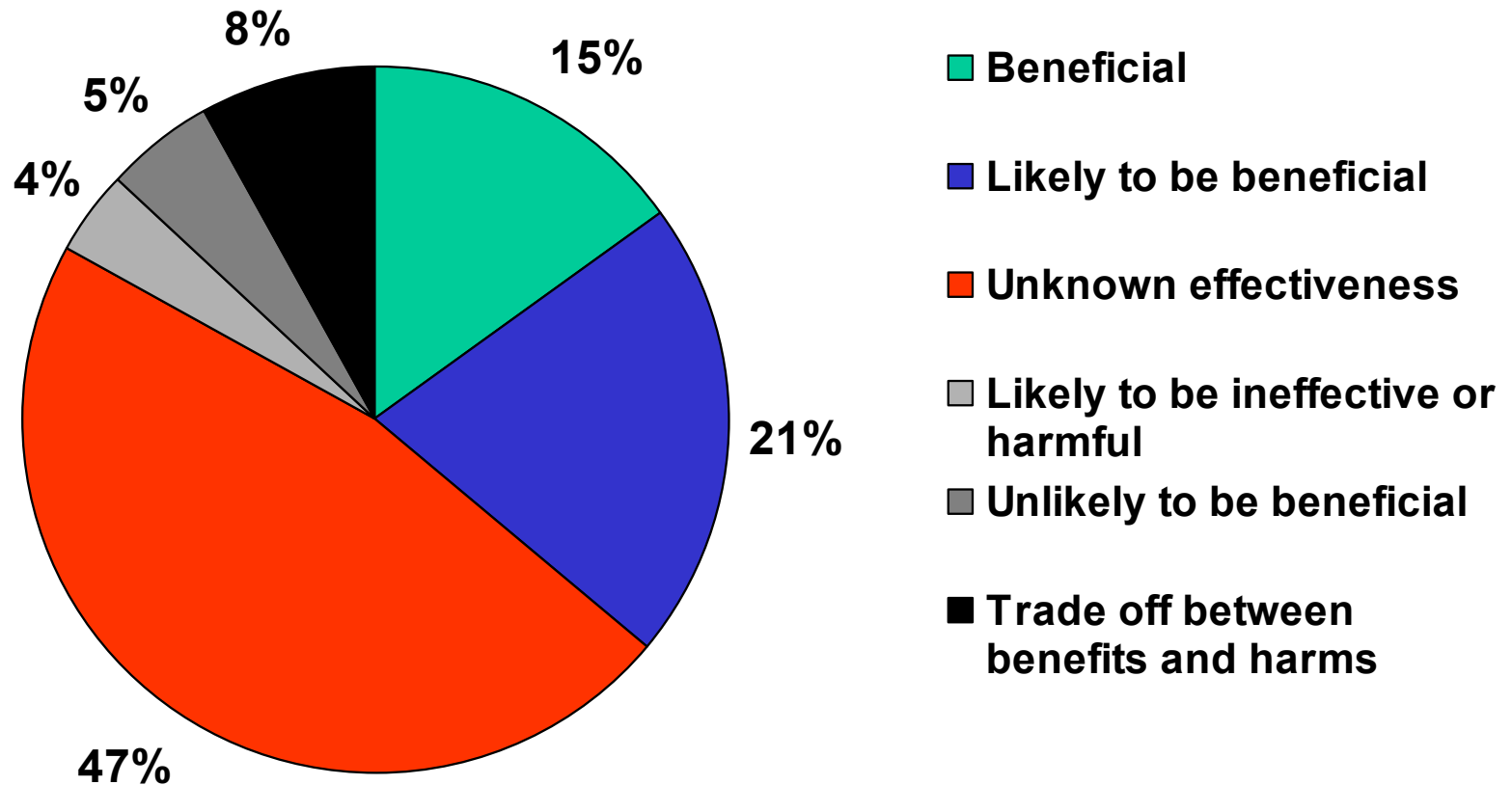
NHS Lothian is considering whether it should continue to pay for homeopathy services. Those against complain that it has no scientific backing and any positive results are due to the "placebo" effect. But homeopathy has ardent supporters who say it has helped them get better and insist it should be available on the NHS.

Homeopathy is a 200-year-old system of treatment that uses very highly diluted substances which are given orally in the belief that they will stimulate the body's self-healing mechanism.

Detractors such as Keir Liddle of Edinburgh Skeptics say homeopathy is "against all the laws of physics and chemistry" because the initial ingredients are so diluted that all that is left is a "memory" in the water.

The British Medical Association, which represents doctors, believes there should be no further NHS funding for homeopathy, saying it is concerned that scarce resources are being spent on a treatment with "no scientific evidence base to support its use".

How much do we know?



Randomised Control Trials

- Comparison against placebos
- Inappropriate controls
- Missing trials

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."

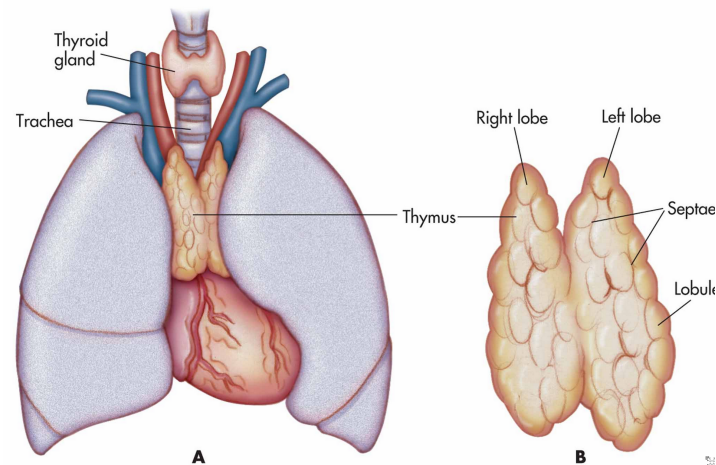
The first book of kings, old testament 500BC

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

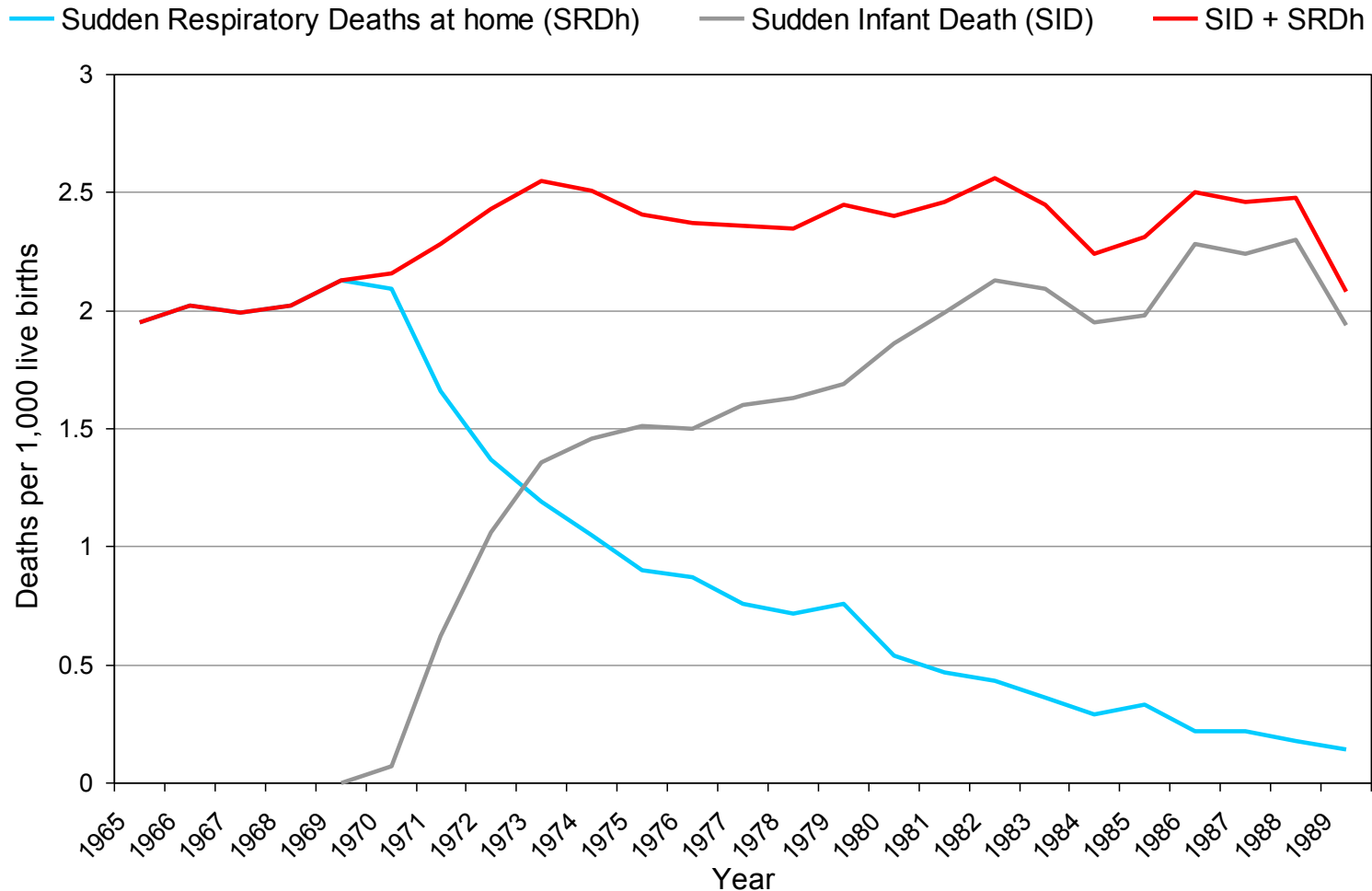
"The sudden death of any infant or young child which is unexpected by history, and in which a thorough post mortem examination fails to demonstrate an adequate cause for death".

– 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		

Odds of exposure in cases = a/c

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
On side or back	5	58
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)
- Thermal insulation/overwrapping

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



The Foundation for the Study of Infant Deaths
114 Hulse Street, London SW1X 7DP
Telephone: 020 7 235 0954
Fax: 020 7 235 1299

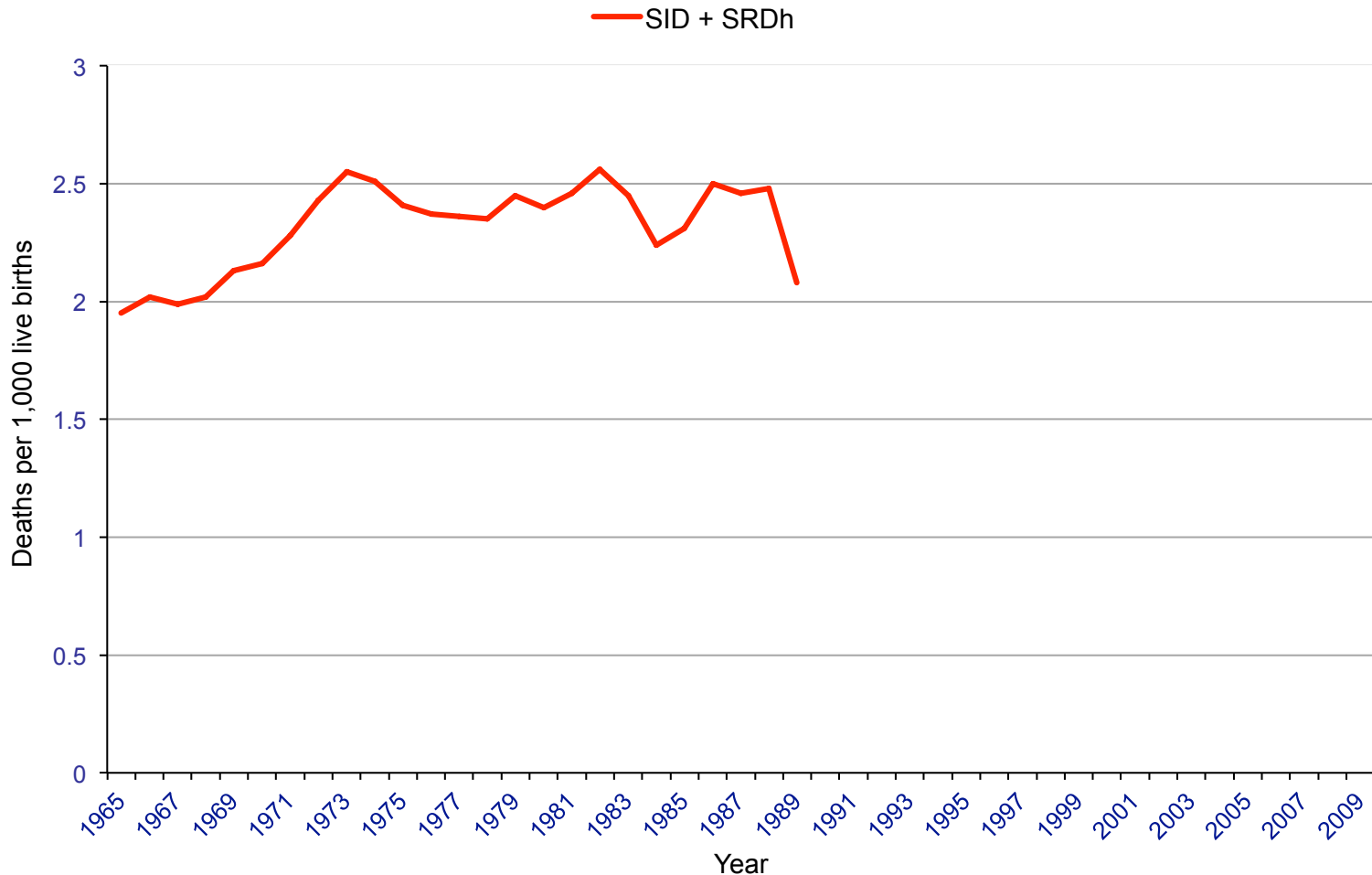


REDUCING THE RISK OF COT DEATH

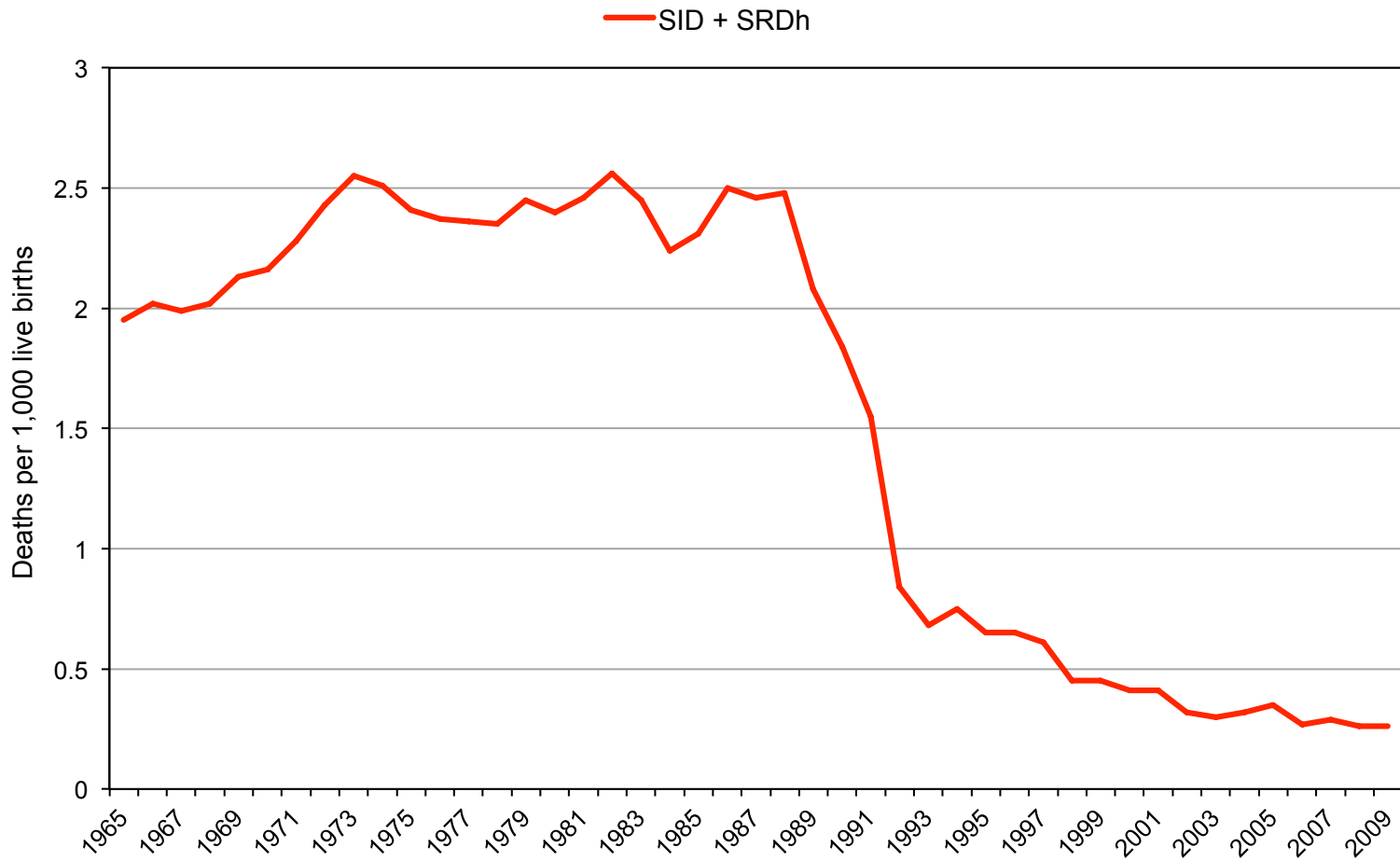
THE DEPARTMENT OF HEALTH

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



Cot death incidence (aged 1 week to 1 year) England and Wales 1965-2009

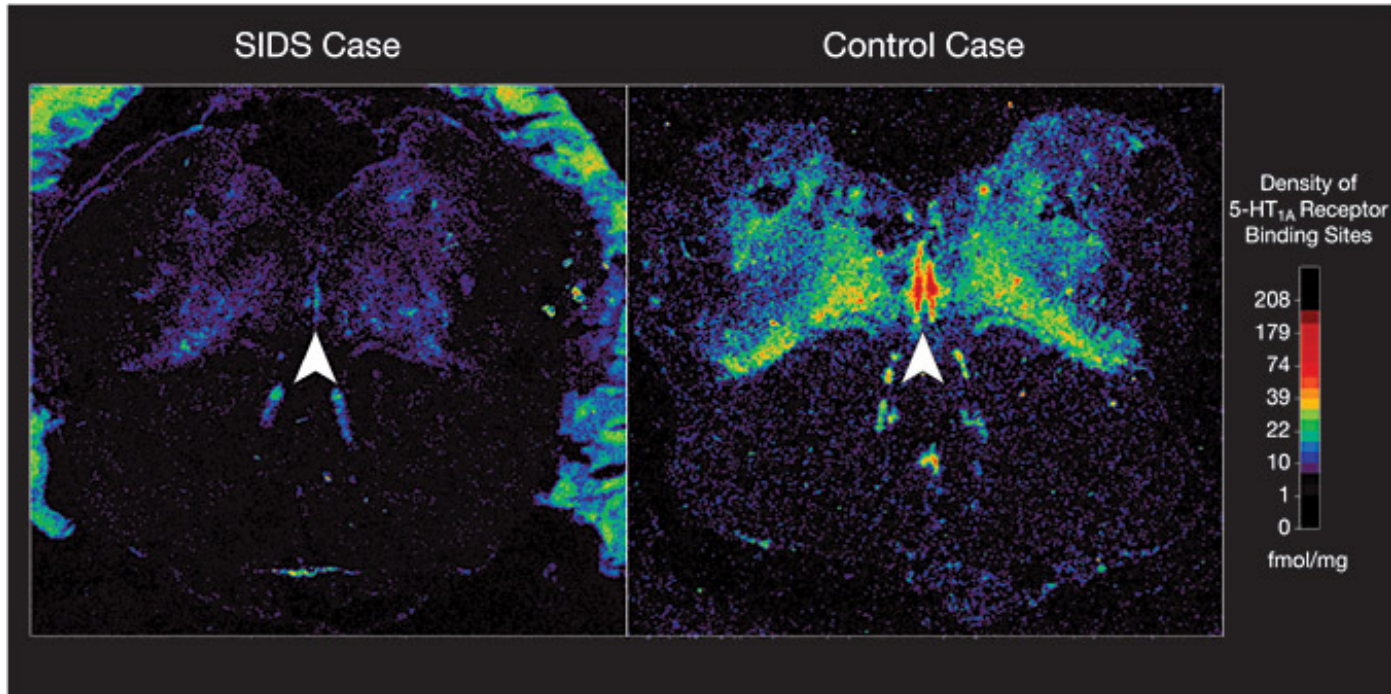


SIDs in England and Wales

- 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-HT_{1A} 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

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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.^{1,2} 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,^{3,7} 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 raphe, lateral extraraphe, and ventral surface and helps regulate autonomic and respiratory function.¹ These medullary nuclei are interconnected⁹ and project extensively to nu-

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 raphe 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

clei 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-

Author Affiliations: Departments of Pathology (Drs Paterson and Kinney and Msrs Thompson, Darnall, and Belliveau) and Pediatrics (Genetics) (Dr Beggs), Children's Hospital Boston and Harvard Medical School, Boston, Mass; New England Research Institutes, Woburn, 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).

For editorial comment see p 2143.

Break

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**

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**

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**

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**

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**

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

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).

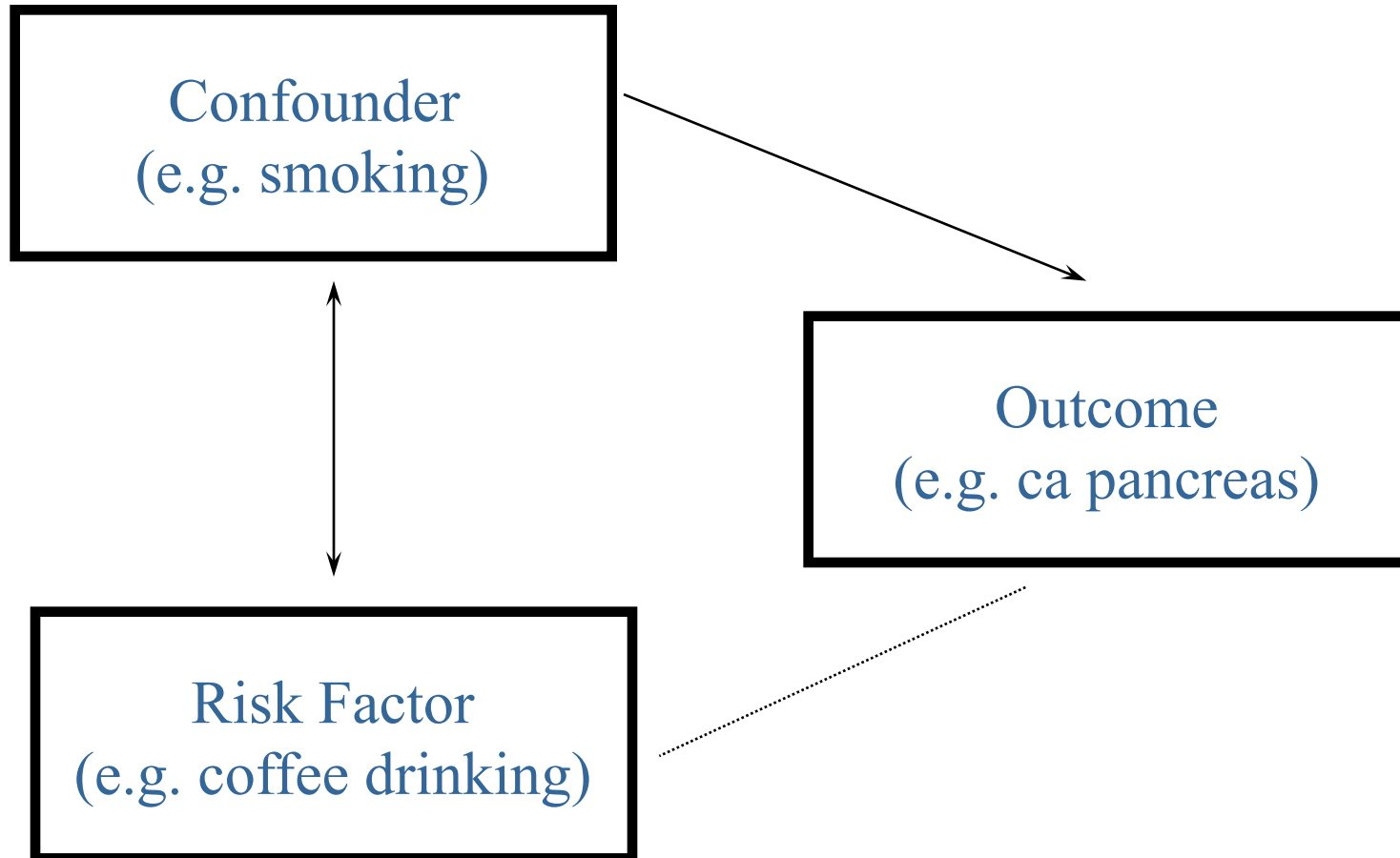
Common confounders

- 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



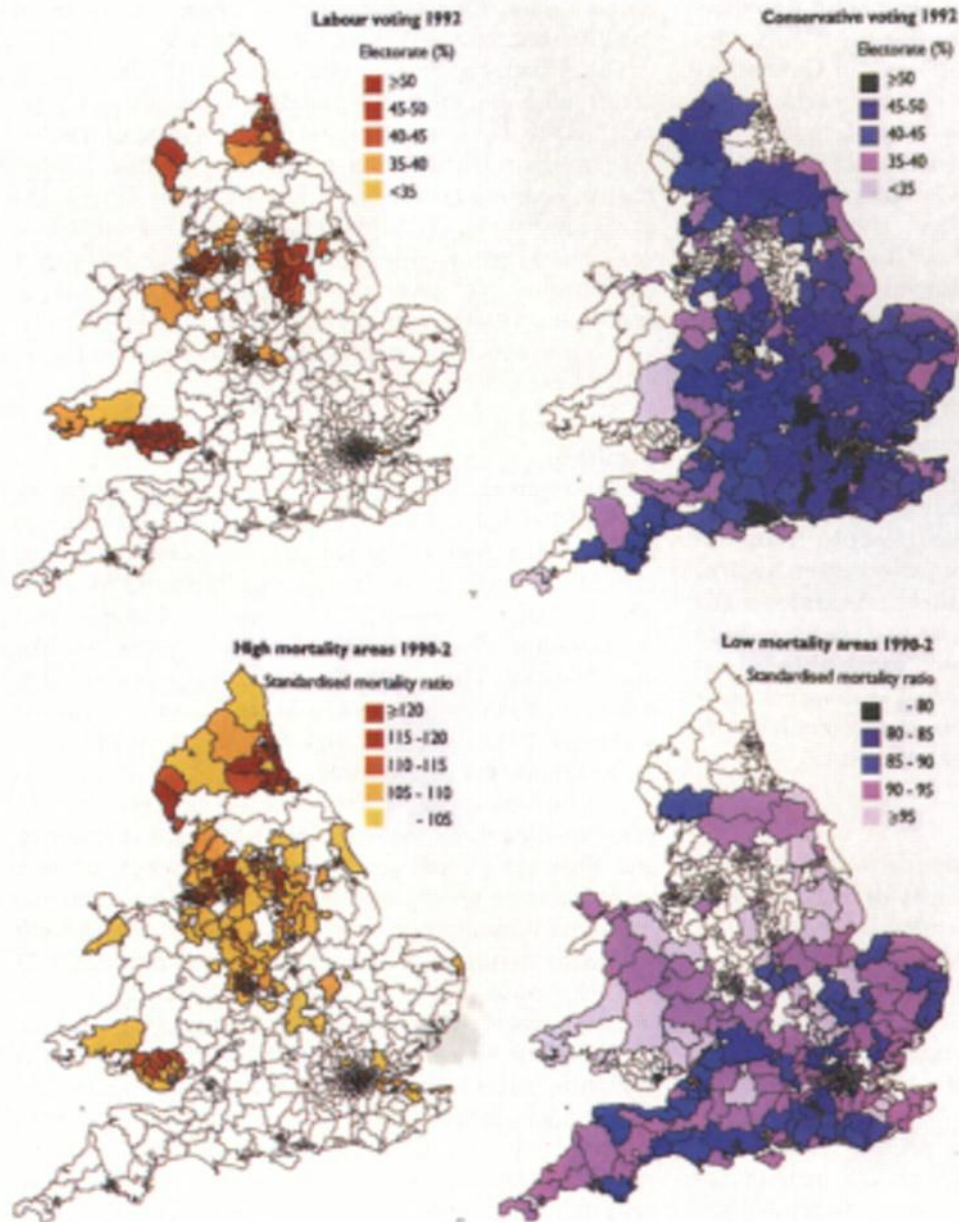


Fig 1—Maps of Labour and Conservative voting in 1992 with maps of high mortality (standardised mortality ratio in white areas <100) and low mortality areas in 1990-2 (standardised mortality ratio in white areas >100)

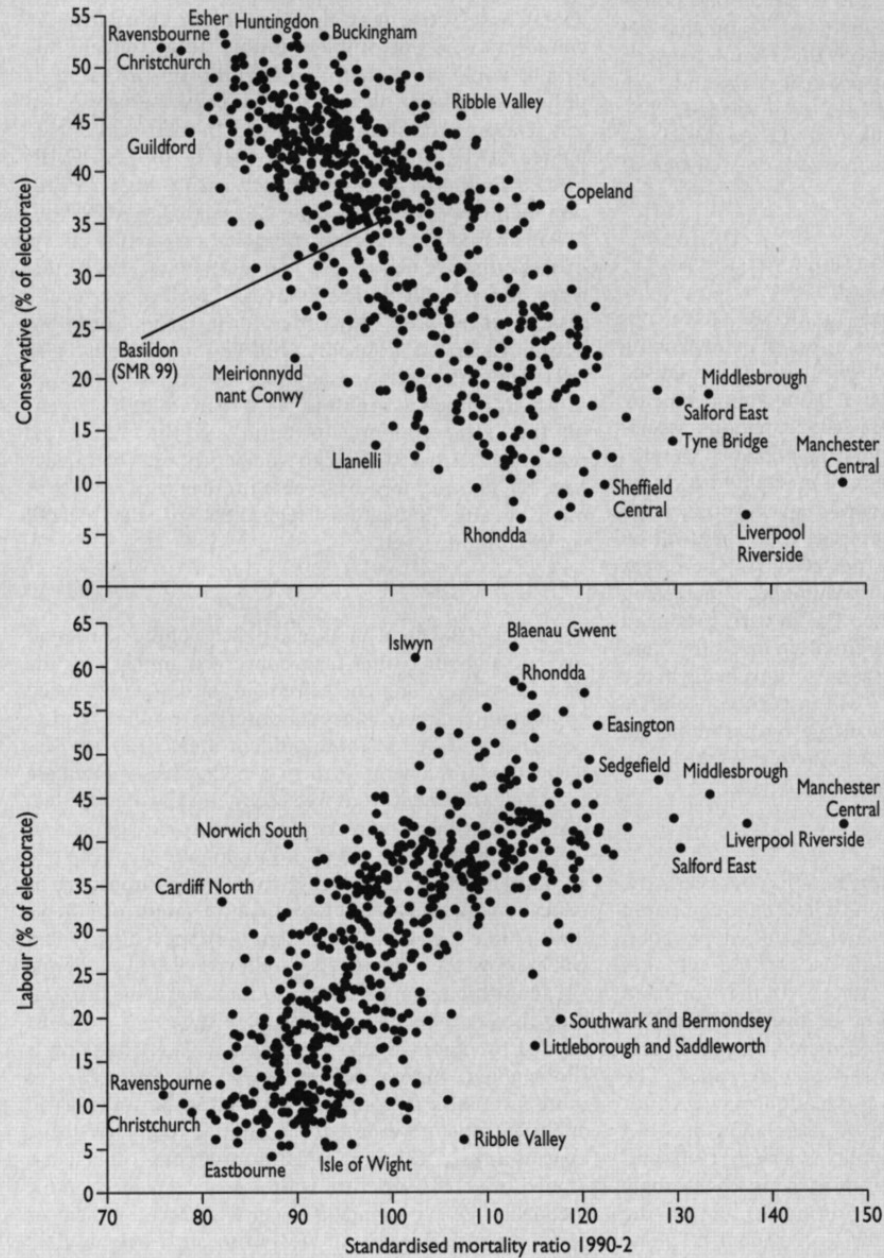


Fig 2—Scatterplots of Conservative and Labour voting in 1992 against all age standardised mortality ratios for 1990-2. SMR = standardised mortality ratio

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

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

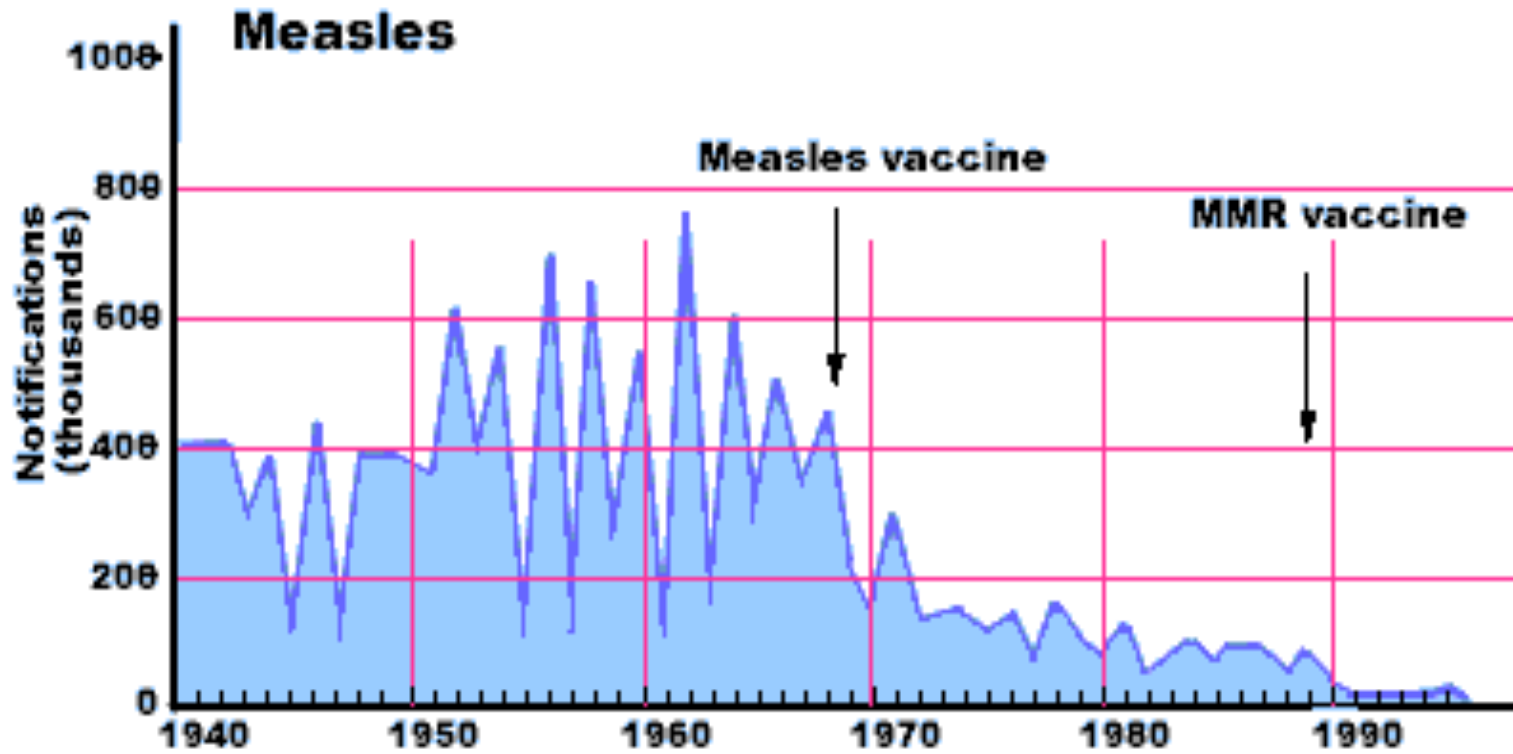
Why is it given?

- 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



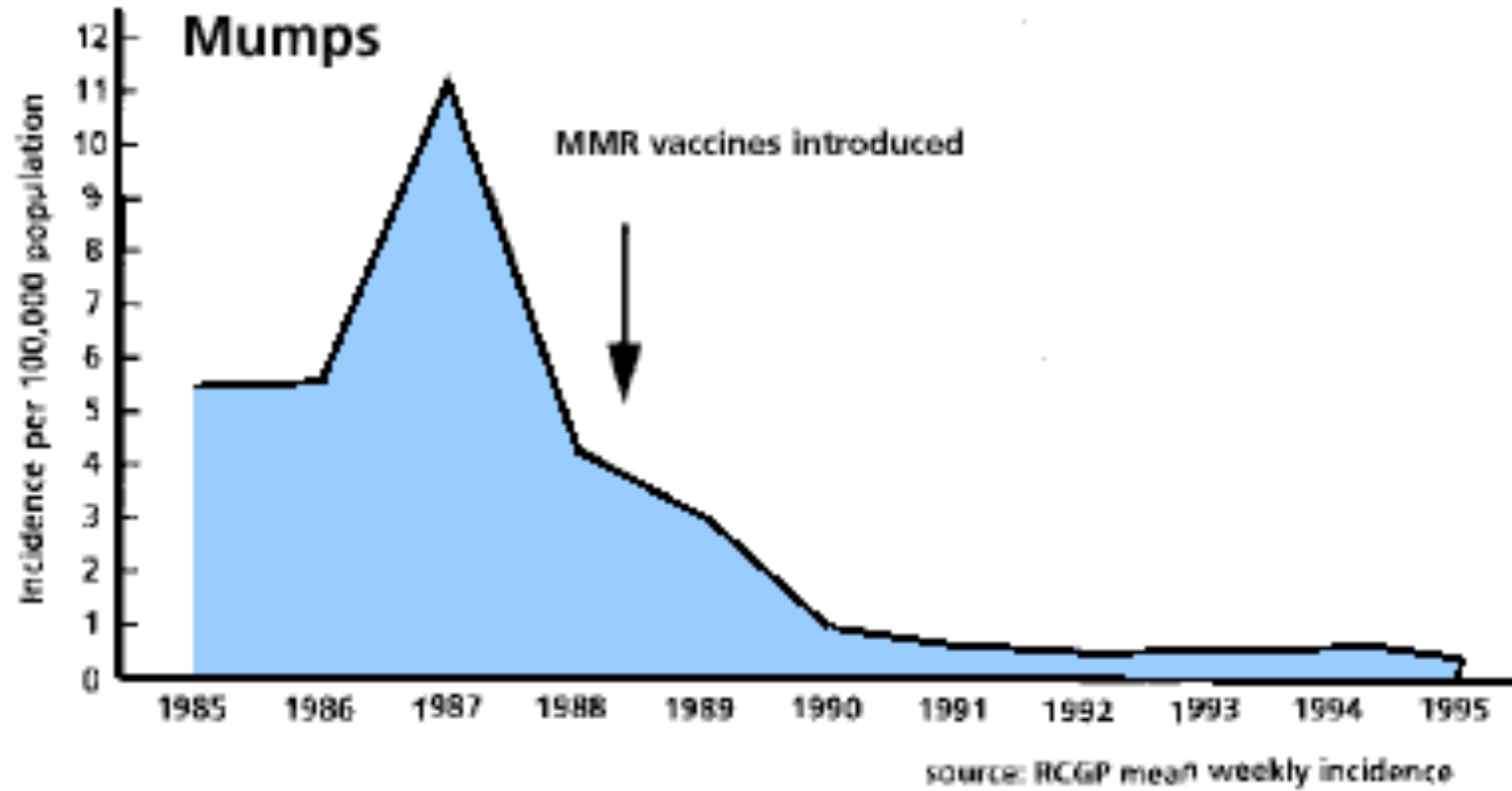
Measles



Mumps



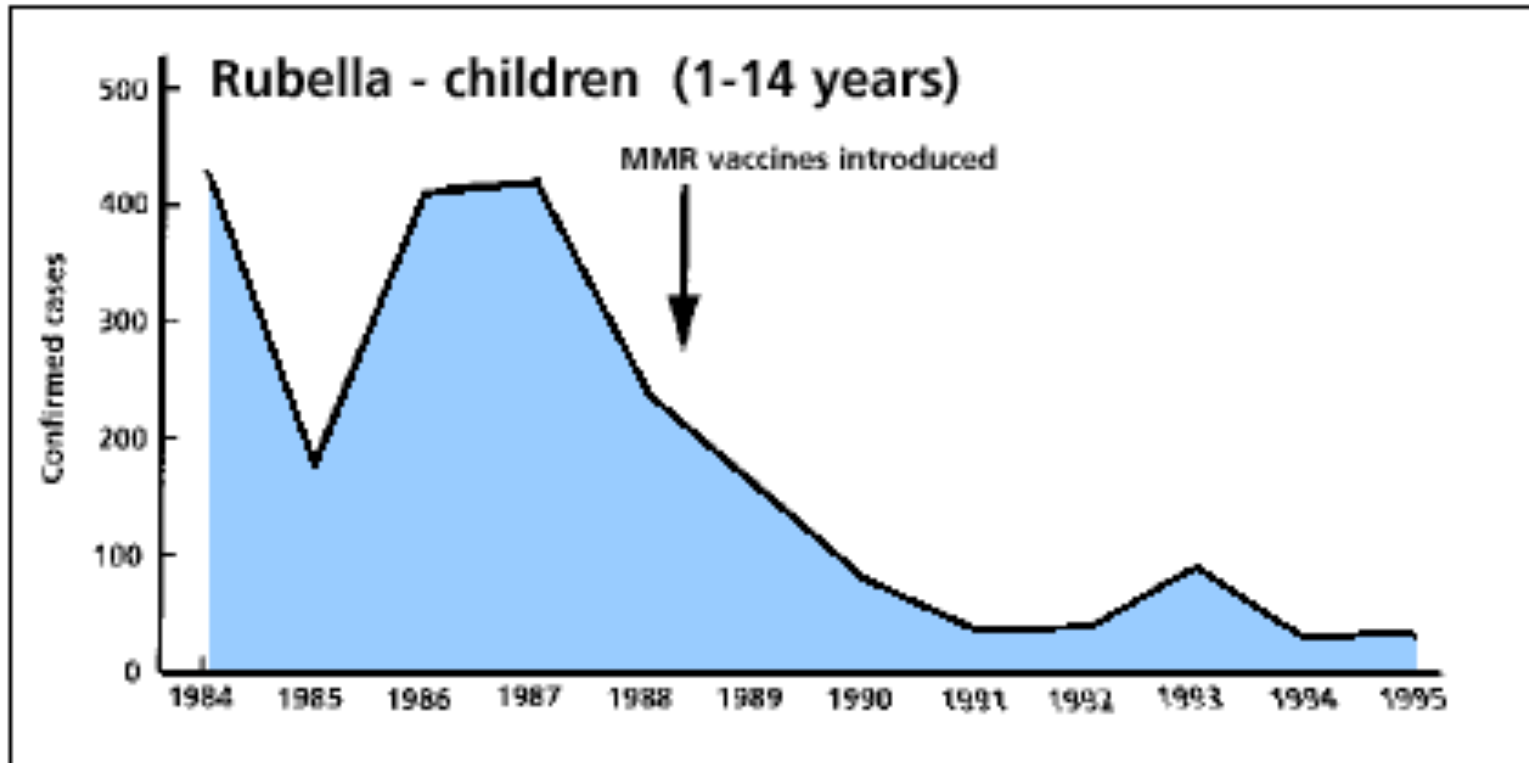
Mumps



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

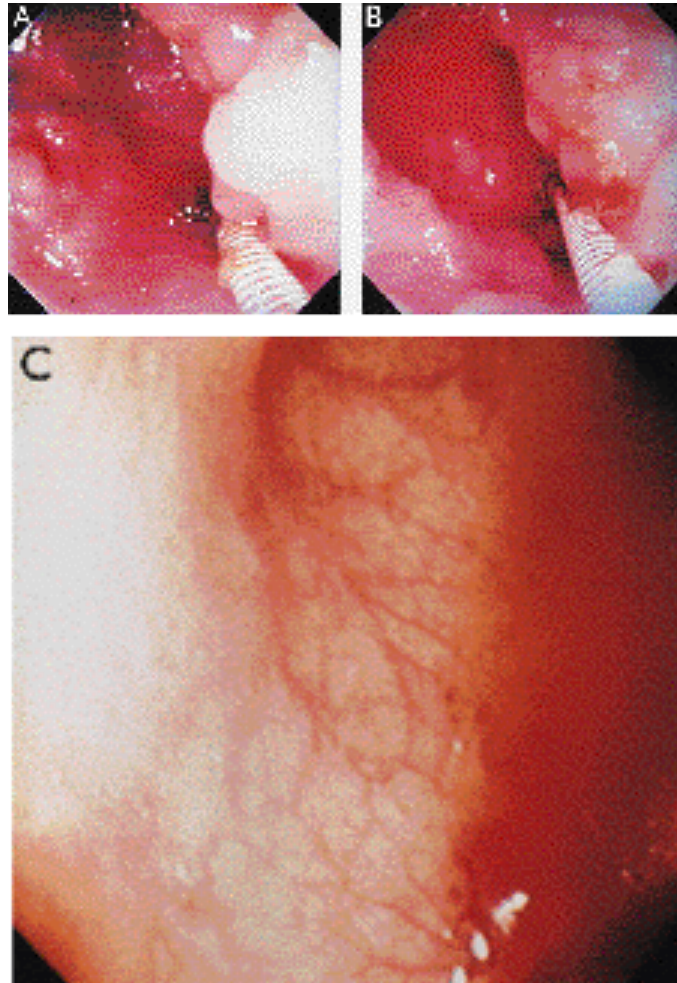
Abstract

- 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”

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



Links

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Welcome to the support group for vaccine-damaged children

Single Jab Clinics

Doctor blames ministers for loss of faith in MMR

London Evening Standard
15 January 2003

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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."

Mumps epidem

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

Dr Mike Fitzpatrick, said: "It is s episode where an unsubst close a major impact on a nation pers

"So much so that a signific withdrawn their children fi Th have a return of diseases

In response to this a snc Great immunisation h

Last Updated: Wednesday, 14 November 2007, E-mail this to a friend

Printa

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 th after research - since discredited MMR and autism.

CHPCT is now using a mobile unit among children.

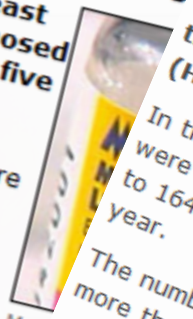
Unfortunate episode

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 the vaccine against the two illnesses.

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



Mea Dr Paul Cleary, of the HPA, said: "Measles and mumps are very infectious and can cause serious complications."

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.

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.

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

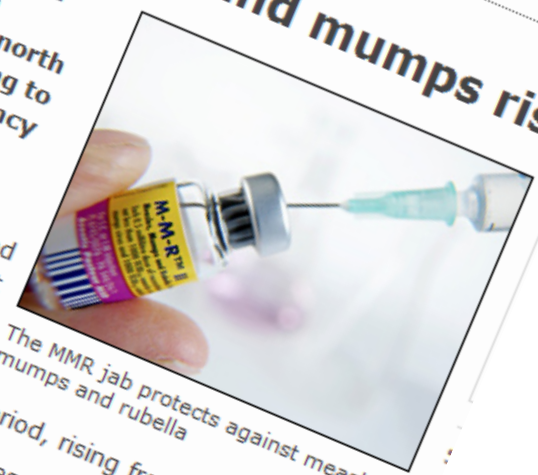
In the North West, Greater Manchester has reported the largest number of measles and mumps cases so far this year.

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.

Fears over measles and mumps rise

Page last updated at 14:17 GMT, Wednesday, 12 August 2009 15:17 UK
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The MMR jab protects against measles, mumps and rubella

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



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[Intervention Review] Vaccines for measles, mumps and rubella in children

 Vittorio Demicheli¹, Tom Jefferson², Alessandro Rivetti³, Deirdre Price⁴
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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

[Next >](#)

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 paper¹ 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, Berelowitz 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.

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MMR doctor struck from register

By Nick Triggle
Health reporter, BBC News

The doctor who first suggested a link between MMR vaccinations and autism is to be struck off the medical register.

The General Medical Council found Dr Andrew Wakefield guilty of serious professional misconduct over the way he carried out his controversial research.

It follows a GMC ruling earlier this year that he had acted unethically.

Dr Wakefield, who is now based in the US, has consistently claimed the allegations are unfair. He now says he will appeal against the verdict.

His 1998 Lancet study caused vaccination rates to plummet, resulting in a rise in measles - but the findings were later discredited.

The GMC ruled in January Dr Wakefield had acted "dishonestly and irresponsibly" in conducting his research, but under its procedures the sanctions are made at a later date.

The case did not investigate whether Dr Wakefield's findings were right or wrong, instead it focused on the methods of research.

During the two-and-a-half-year case, the longest in GMC history, he was accused of carrying out invasive tests on vulnerable children which were against their best interests.

The GMC also said Dr Wakefield, who was working at London's Royal Free Hospital as a gastroenterologist at the time, did not have the ethical approval or relevant qualifications for such tests.

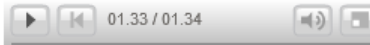
And the panel hearing the case took exception with the way he gathered blood samples. Dr Wakefield paid children £5 for the samples at his son's birthday party.

It also said Dr Wakefield should have disclosed the fact that he had been paid to advise solicitors acting for parents who believed their children had been harmed by the MMR.

Serious misconduct

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MMR vaccine row doctor defends...
The doctor who first suggested a link



MMR vaccine row doctor defends investigation

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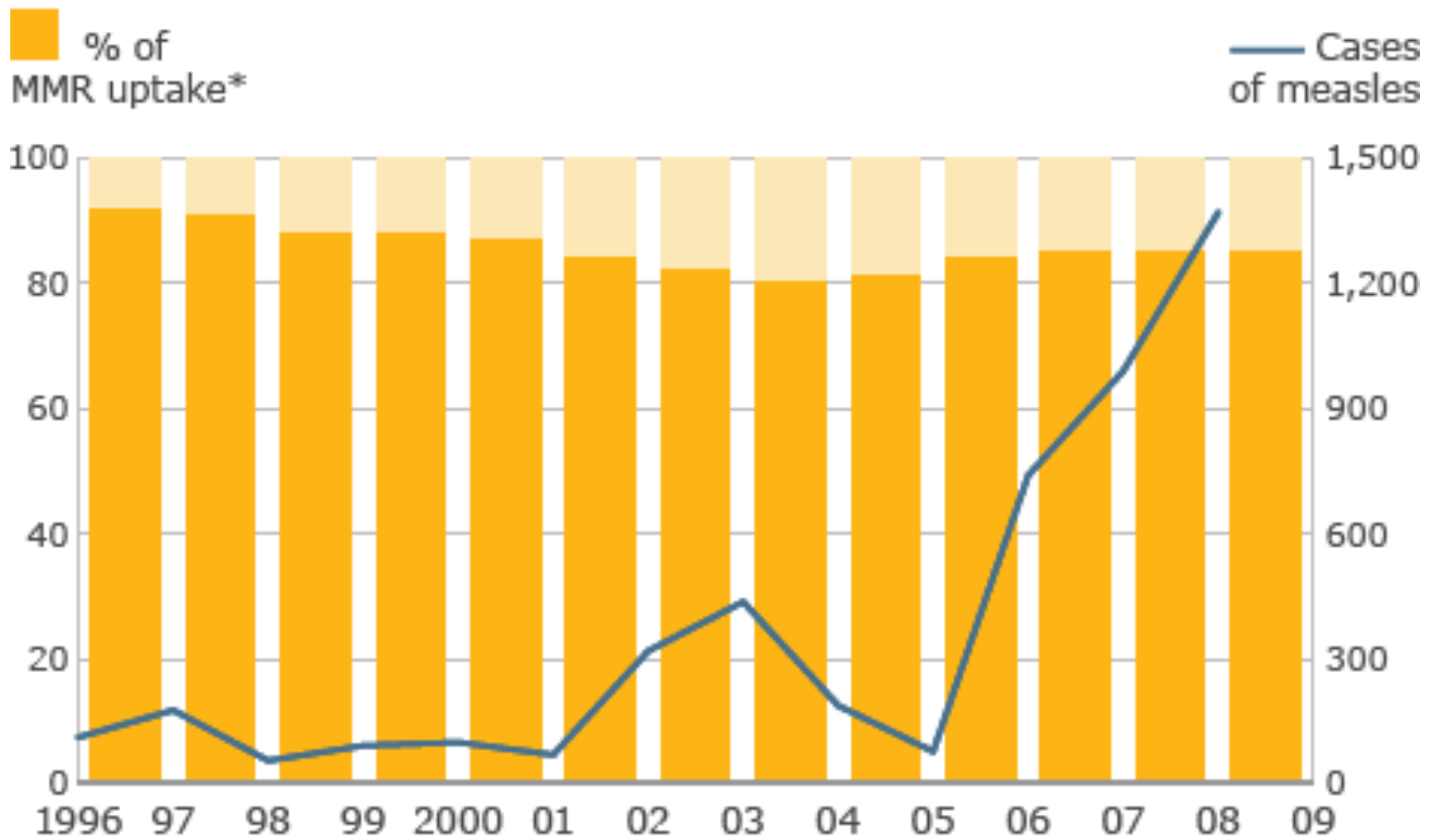
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Andrew Wakefield

- “My responsibility is to the individual patient”

MMR and measles



*figures relate to financial years 1996/97, 1997/98 etc

Source: HPA

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

1 March 2013 Last updated at 10:01



Measles : Vaccination call after south west Wales outbreak

People who may be at risk of measles are being urged to have the MMR vaccine following an outbreak in south west Wales.

There have been a reported 189 cases of the infection in Swansea and Neath-Port Talbot since November, more than the whole of Wales in the past three years.

Doctors say anybody who is not sure whether they have had measles or been vaccinated should have the MMR jab.

They said there is no upper age limit for the vaccine.

The outbreak so far only affects the Abertawe Bro Morgannwg University Health Board area, where 32 secondary schools, primary schools and nurseries are affected.

Public Health Wales estimates there are more than 8,500 schoolchildren at risk of measles in the area.

Dr Matthew Snape, a consultant in vaccinology and general paediatrics from Oxford University, said anybody who had not had the MMR jab was at "serious risk".

He said many children missed out on the vaccine following the now-discredited 1998 report linking the MMR jab and autism and the vaccination rate dropped from 90% to 80%. It is now back to around 92%.

Children should receive the first dose of the vaccine at 12 to 13 months of age and the second at three years and four months of age.

But Dr Snape he said it was not too late to have the vaccine: "There's no upper age limit so parents can still take their child to the GP. That's what they should be doing to be honest, especially if it is now circulating again.

"Measles is still a very dangerous infection. It's not something that's a right of passage of



A blotchy rash appears a few days after someone is infected with measles

Related Stories

[Concern as measles outbreak hits 189](#)

[Rise in measles cases in Wales](#)

[Measles cases 'almost double'](#)

MEASLES FACTS

- It is a highly infectious viral illness
- It causes a fever, coughing and distinctive red-brown spots on the skin
- You catch measles by breathing in tiny droplets created when an infected person coughs or sneezes
- Possible complications include pneumonia, ear and eye infections and croup
- Serious complications include inflammation of the brain (encephalitis), which can be fatal
- Measles in pregnancy can cause miscarriage, premature labour or a baby with low birth weight
- The most effective way of preventing measles is the measles, mumps and rubella (MMR) vaccine
- There is no link between the MMR vaccine and autism

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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 decision making

Further reading

