

Vaccination paper retracted

# Pushed from the Published Record

Recently, the medical journal *The Lancet* has retracted a 12 year old controversial publication, which culminated in the 'Measles Mumps Rubella' (MMR) vaccine safety scare. Obviously, it was flawed.

After 12 years of dispute, the medical journal *The Lancet* fully retracted a publication by gastroenterologist Andrew Wakefield and co-authors, which suggested a potential association between the combined measles, mumps and rubella vaccination (MMR) with intestinal problems and the onset of autism. The study titled 'Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children' investigated only 12 patients (*The Lancet* 351: 637-641, 1998). The publication and an ensuing press conference sparked widespread coverage by the media and thus undermined public confidence in the MMR vaccine. As a consequence, vaccination rates plummeted and measles surged from 56 cases in England and Wales in 1998 to 1,370 cases in 2008. Currently, in the UK, one in five children is not fully vaccinated with the MMR vaccine at the age of five. In 2006, the first child in over a decade died of measles.

The retraction of the publication in February 2010 followed the judgement of the

General Medical Council's Fitness to Practise Panel. The General Medical Council licenses doctors to practise medicine in the UK. At the time of the study, Wakefield worked as a Senior Lecturer, Reader and Honorary Consultant in Experimental Gastroenterology at the Royal Free Hospital in London. Co-authors John Walker-Smith and Simon Murch were a Professor of and a Senior Lecturer in paediatric gastroenterology at the Royal Free Hospital, respectively.

## Misleading descriptions

The Panel ruled that the publication by Wakefield *et al.* from 1998 gave a misleading description of the patient population and of the referral of patients. In the 'Patients and methods' section, the publication stated that the children were consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms. It did not disclose that some of the patients had no history of gastrointestinal symptoms



With a flawed paper Andrew Wakefield caused a dramatic drop of MMR vaccination rates in the UK.

and that the authors, Wakefield and Walker-Smith, were actively involved in the recruitment of children for the study, which suggests a biased selection of patients. *The Lancet* publication also wrongly stated that investigations had been approved by the Ethical Practices Committee of the Royal Free Hospital NHS Trust. According to the panel's findings, investigations of children, including invasive procedures such as colonoscopy and lumbar puncture, were performed without ethical approval and without being clinically indicated.

The panel found that Wakefield breached rules of research funds management. Additionally, he did not properly disclose 'conflict of interest' to the local Ethics Committee and to *The Lancet* in connec-

tion with the retracted study, raising further doubts about the study's impartiality. Wakefield concealed his involvement in advising "a solicitor acting for persons alleged to have suffered harm caused by the administration of the MMR vaccine, as to the research that would be required to establish that the vaccine was causing injury". He did not mention that he received £50,000 of funding from the Legal Aid Board, for which he examined the presence or absence of the measles virus in intestinal tissue of autistic children and appropriate controls. Wakefield also should have disclosed *The Lancet* as a 'conflict of interest' that he had previously filed a patent application in 1997. The invention related to a new MMR and measles vaccine and to a pharmaceutical or therapeutic composition for the treatment of inflammatory bowel disease, particularly Crohn's disease and ulcerative colitis and regressive behavioural disease.

### Ethical approval defied

The Panel found that Wakefield, Walker-Smith and Murch acted contrary to the clinical interests of patients and that they defied the conditions of ethical approval when performing their study. Wakefield ordered investigations without having the requisite paediatric qualifications and although his honorary consultant appointment excluded any involvement in the clinical management of patients. He also raised public attention by having blood samples collected from a group of children at his son's birthday party for research purposes without ethical approval. Those children who gave blood received £5 at the end of the party. A

video on the BBC website showed him joking at a conference in 1999. He recounted, "[...] so these are your perfect controls, so we lined them up with informed parental consent of course...and they put their arms out with a cuff on and have the blood taken. It's all entirely voluntary. When we did this at that party two children fainted, one threw up over his mother [...]."

### Reservations from the beginning

In April, the panel will further investigate whether sanctions should be imposed on Wakefield's, Walker-Smith's and Murch's registrations in the UK. After the Panel's judgement, Wakefield declared his extreme disappointment at the outcome, maintaining that the allegations against him and his colleagues were both unfounded and unjust. He expressed his dismay that his colleagues Walker-Smith and Murch had been dragged through this process.

Because of their preliminary nature, the findings of Wakefield and co-authors were published in 1998 as an 'Early Report'. In the publication, the authors stated cautiously that they "did not prove an association between measles, mumps, and rubella vaccine and the syndrome described. [...] Further investigations are needed to examine this syndrome and its possible relation to this vaccine". Furthermore, Wakefield's publication was accompanied by a critical comment from vaccine experts Robert Chen and Frank DeStefano from the US Centers for Disease Control and Prevention (*The Lancet* 351: 611-12, 1998). They doubted a causal relationship between MMR, bowel disease and autism because hundreds of

millions of people vaccinated against measles did *not* develop chronic bowel or behavioural problems. They argued that if MMR caused the described syndrome, it did so extremely rarely. Chen and DeStefano criticised the lack of supportive virological studies and supposed that patients had been recruited in a biased manner.

They argued that vaccine-safety concerns gained prominence when the incidence of vaccine-preventable diseases fell to negligible levels and when the number of vaccine adverse events, whether true reactions or only coincidental, rose as a consequence of high vaccine coverage. In a visionary manner they warned that vaccine-safety concerns, such as that reported by Wakefield and colleagues, might snowball into societal tragedies when the media and the public confused association with causality and shunned immunisation.

### A fateful press release

Despite the lack of scientific evidence, Wakefield recommended in a subsequent press release that children should be vaccinated with separate vaccines against mumps, measles and rubella spaced out by at least a year, and not with a combined MMR vaccine, until further research was done. However, the majority opinion among the researchers involved in the study supported the continuation of the MMR vaccination, the press release stated. Picked up by the media, Wakefield's suggestion sparked an immense vaccine safety scare. His scare-mongering was taken as a recommendation to parents not to have their children vaccinated at all until individual vaccines were

## Retraction—ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Following the judgment of the UK General Medical Council's Fitness to Practise Panel on Jan 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al<sup>1</sup> are incorrect, contrary to the findings of an earlier investigation.<sup>2</sup> In particular, the claims in the original paper that children were "consecutively referred" and that investigations were "approved" by the local ethics committee have been

proven to be false. Therefore we fully retract this paper from the published record.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.
- 2 Hodgson H. A statement by The Royal Free and University College Medical School and The Royal Free Hampstead NHS Trust. *Lancet* 2004; **363**: 824.

obtainable, as *The Lancet* Editor Richard Horton wrote in *MMR – Science and Fiction* (Granta Books, London, 2004). However, single antigen vaccines were only obtainable on a private basis and, therefore, only a minority of parents made use of this possibility.

The live MMR vaccine had been introduced in the UK in 1988 and replaced single vaccines. Prior to its release, no studies had been performed to look for autism after vaccination, David Elliman and Helen Bedford reported in their article 'MMR: where are we now?' (*Arch. Dis. Child.* 92: 1055-1057, 2007). However, there were no concerns in this respect after 16 years of use of the vaccine in the USA. Autism is also not observed after postnatal measles, mumps or rubella, unless accompanied by severe encephalitis. In 1992, brands of MMR vaccine containing the Urabe strain of the mumps vaccine virus were withdrawn after it had been found to be associated with an increased risk of aseptic meningitis. In 1997, an additional MMR vaccine brand was introduced in the UK. Numerous studies have corroborated the safety of the MMR vaccine and found no scientific evidence of an involvement of the vaccine with autism or inflammatory bowel disease. Worldwide, over 500 million doses of MMR vaccine have been used since the early 1970s.

### Retraction seemed overdue

In February 2004, Brian Deer, a journalist for the *Sunday Times*, made allegations against Wakefield in a meeting with editors of *The Lancet*, Horton reported in *MMR – Science and Fiction*. Deer's findings suggested that Wakefield and his colleagues had conducted invasive investigations on children without ethical approval and that the children for the study were cherry-picked to fit a preconceived theory linking the MMR vaccine to autism. Deer's presentation and Wakefield's subsequent admission also

gave the impression that Wakefield had concealed a 'conflict of interest' by being a paid advisor in a MMR litigation matter. Some of the children in *The Lancet* publication were also part of the litigation-driven research. Deer's allegations precipitated investigations by the General Medical Council.

*The Lancet* concluded in March 2004, after own investigations into the allegations, that Ethics Committee approval had been granted and that there was no active biased selection of patients for the study. However, Wakefield should have disclosed the existing 'conflict of interest'. The journal's guidelines at the time stated, "The conflict of interest test is a simple one. Is there anything...that would embarrass you if it were to emerge after publication and you had not declared it?" Subsequently, 10 of the publication's 13 authors, including Walker-Smith and Murch, retracted the most controversial part of the publication, the interpretation expressed about a possible link between the MMR vaccine and autism. Nearly six years later, after the hearing of the General Med-

ical Council's Fitness to Practise Panel, *The Lancet* decided to fully retract the paper from the published record. "Although the retraction seems overdue, it can only be a good thing for science," Trisha Greenhalgh, Professor of Primary Health Care at University College London, commented in the *BMJ* (340:c644, 2010).

### Ongoing investigations

The General Medical Council's investigation will continue in April and may have different repercussions for the three physicians. Murch, a Professor of Paediatrics and Child Health at the University of Warwick, is the only one working in the UK and, therefore, would be affected the most by any sanctions enforced by the General Medical Council's Fitness to Practise Panel. Walker-Smith is retired. Wakefield left the Royal Free School of Medicine in 2001 and lives and works now in the US. He is one of the founders and Executive Director of 'Thoughtful House', a centre for children with developmental disorders in Texas, which combines medical care, education and research. The centre supports a "safety-first vaccination policy" and recommends that "parents with questions or concerns about a particular vaccination should discuss it with their child's doctor". The centre's website tells that research into a possible link between the MMR vaccine and autism is ongoing. Studies include the analysis of childhood vaccinations and regressive autism in rhesus macaques.

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## One fine day in the lab...

by Leonid Schneider

