

**Dr CM Stott 5<sup>th</sup> November 2004**

**Comment on ‘A Critical Appraisal of the Wakefield et al paper’ Professor Trisha Greenhalgh**

**<http://briandeer.com/mmr/lancet-greenhalgh.htm>**

In a recent communication from the UK Department of Health a concerned parent was told that it was in the public interest for the much visited NHS Web-site ‘MMR The Facts’ to link with the website of a freelance investigative journalist, Mr Brian Deer. A particular advantage of the link, claimed the DoH correspondent concerned, was that it provides easy access to Professor Trisha Greenhalgh’s critical appraisal of the Lancet paper - Wakefield et al. 1998 - ‘Ileal-lymphoid-nodular-hyperplasia, non-specific colitis and pervasive developmental disorder in children.’ (URL above). This suggests that the NHS executive holds Professor Greenhalgh’s appraisal in significantly high regard. On reading the document therefore, it was rather disconcerting to note the presence of fundamental errors and a patent unfamiliarity with basic epidemiological principles.

Most introductory epidemiological textbooks outline five basic study designs as follows: case-series (clinic or population), cross-sectional studies, case-control studies, cohort studies (prospective and retrospective) and trials (see for example Bhopal, 2002). These study designs are used variably to address specific research issues, from descriptions of a particular presentation or set of presentations (as in a case-series) to analytical interpretations facilitating identification of causal factors (as in a case-control study).

The first line of the Wakefield et al. (1998) paper states its design as ‘...a consecutive series of children with chronic entero-colitis and regressive developmental disorder.’ In other words the study is a case-series. A typical example of how basic epidemiological textbooks define and describe a case-series can be found in Hennekens and Buring, (1987): (my emphasis)

*‘Case-series studies **describe** the experience of a single patient or a **group of patients** with a **similar diagnosis**. These types of study, in which typically **an astute clinician** identifies **an unusual feature of a disease** or a patient’s history, may lead to **formulation***

*of a new hypothesis..... At that time an analytic study (most frequently using a case-control approach), can [then] be done to investigate possible causal factors'.*

Hennekens and Buring (1987) thus make a perfectly simple but crucial point, that the purpose of a case-series is to describe specific presentations and to **generate** new hypotheses about potential causation. They are not designed to investigate possible causality. Let us now turn to Professor Greenhalgh's treatment of the Wakefield et al (1998) case-series with these factors in mind, using the critical appraisal checklist she provides:

**1 Is the topic area important and relevant to the Lancet's readership?**

In response to this question, Professor Greenhalgh refers to the rise in 'incidence of autism' at around the time the Lancet paper was published. It should be pointed out that virtually no data on incidence change in autism or autism spectrum disorders were available at that time. Professor Greenhalgh has no doubt confused incidence with prevalence in making an otherwise valid point.

**2 Was the study original?**

Professor Greenhalgh concludes, quite reasonably, that it was. However, she goes on to state that the study's originality derived from its exploration of a link between MMR vaccine, bowel problems and autism in children. The study did not explore such a link nor did it claim to do so. The study 'investigated a consecutive series of children with chronic entero-colitis and regressive developmental disorder' and in so doing, made the observation that a number of children who appeared to present with similar features also appeared to share a similar exposure history.

**3 Was the research hypothesis clearly stated?**

Professor Greenhalgh concludes that the hypothesis was not clearly stated, saying 'The paper does not state a research hypothesis at all'. This is quite true. Case-series studies are neither required nor expected to do so. In the absence of such a hypothesis Professor Greenhalgh, however, having obviously misunderstood the study design by this stage, provides us with her own.

#### 4 What was the study design?

On reading Professor Greenhalgh's response to this question, it appears that she has now grasped what the study intended, as she quite accurately refers to it as 'a descriptive report' and provides some detail of the methodology and testing that took place.

#### 5 Was this design an appropriate way to test the research hypothesis?

Professor Greenhalgh concludes that the study design was not an appropriate way to test 'the research hypothesis'. However, as she has already said that no hypothesis was originally stated, it rather begs the question of which hypothesis the study was not designed to test. It soon becomes clear, as Professor Greenhalgh goes on to explain in some detail why the Wakefield et al. (1998) study did not address *her* hypothesis. The final conclusion that '*the study design was incapable of proving that link one way or the other*' is of course, entirely accurate as indicated by the study authors themselves on p641, para 2, lines 1 and 2 :'*We did not prove an association between measles, mumps and rubella vaccine and the syndrome described...*' and para 5, lines 4-6 '*Further investigations are needed to examine this syndrome and its possible relation to the vaccine.*'

#### 6 Were the study's conclusions supported by the data?

This is a rather confusing point as it is not entirely clear whether Professor Greenhalgh is referring to the *authors* conclusions – i.e. that the data do not demonstrate a causal link between the disorder and MMR exposure, or whether she is asking if the data support her own hypothesis. In the former case, the data clearly support the author's conclusions. Not surprisingly, they do not support Professor Greenhalgh's hypothesis. It is interesting to observe the choice of language here. Rather than referring to what is actually stated in the paper (i.e. no proven association) she chooses instead to focus on '...the overall '*tone*' of the paper, [which] strongly *suggests* that they *believed* they had demonstrated a link [between MMR vaccine and autism-bowel syndrome]. This is a little bizarre to say the least. Most scientists would be very wary of attempting to guess what researchers were trying to suggest they believed, particularly when there is no contemporaneous contact between the critic and the researchers in question.

**7 If the answer to (5) is no, would a more robust study design have been practically possible to test the study's main hypothesis.**

This is also a rather confusing point as Professor Greenhalgh has again inserted her own hypothesis into the appraisal. To clarify, it seems that she is asking whether it is theoretically possible to carry out a robust study into the putative association between exposure to polyvalent measles-containing vaccine (pMCV) and the phenotype of interest. Most certainly, yes, she concludes. Unsurprisingly.

The final points made by Professor Greenhalgh refer to several subsequent studies, all 'much larger and better designed than Wakefield's'. In this assertion there lies an implicit assumption that these studies had directly comparable shared aims with the case-series, which of course they did not. It would hardly be feasible for example to conceive of a case-series comprising 1.8 million children, although. I would be interested to learn about any of which Professor Greenhalgh is aware. The large-scale epidemiological case-control or cohort studies generally cited in this context are indeed larger than the Wakefield et al study, but they are not necessarily 'better designed'. The two cited studies, for example, have received extensive criticisms.

It is the case, nonetheless, that no large-scale epidemiological studies to date have demonstrated a significant effect of exposure to pMCV on increased risk of autistic-like developmental regression and associated gastro-intestinal pathology. One of the criticisms often made of such studies is that they have been insufficiently powered to detect a difference between exposure rates in cases and controls (case-control studies), or in ASD or non-ASD outcome in exposed and unexposed groups (cohort studies). The failure to detect any effect may well derive in part from the persistent tendency of these studies to misinterpret the original 'Wakefield hypothesis' that was generated after the publication of the 1998 Lancet paper. This has led to ascertainment errors in study design whereby the phenotype of interest (developmental regression) has almost invariably been swamped by more generic ASD presentations in case groups.

The authors of the recently published paper (Smeeth et al. 2004), for example, state on page 967 that they '*...were not able to separately identify a sub-group of cases with regressive symptoms to investigate the hypothesis that only some children are vulnerable to MMR induced disease...*' In other words, they too failed to test the right hypothesis.

In this context a reasonable question might be framed as follows:

If the so-called ‘Wakefield hypothesis’ is accurate; if the proposed phenotype is valid and if there is indeed cause for concern with regard to a specific and small sub-group of ASD children, have *any* of the epidemiological studies to date been designed sufficiently well to give them a reasonable chance of detecting the proposed association?

No epidemiological study to date has satisfied me on this point. Nor had any epidemiological study satisfied Professor Sir Michael Rutter on the same point when he stated at the Novartis Foundation Symposium (September 2003) that:

*“...as I read the epidemiological evidence there is no real support for MMR being a cause of the rise in autism. Whether it is responsible for a small number of individual cases is an entirely separate question”* (Rutter , 2003).

That Professor Greenhalgh herself *does* appear satisfied on the basis of what can only be described as a complete misunderstanding of the Wakefield et al. (1998) study design is a cause for concern. The failure of the NHS executive to appreciate the potential impact of this fundamentally flawed document on the understanding of many thousands of worried parents is nothing short of a disgrace.

Perhaps the final word should help us re-consider the potential usefulness of initial case-series data in generating appropriate hypotheses:

*‘Clinical situations in which a case report or case series is an appropriate type of study include the following:*

*A doctor notices that two babies born in his hospital have absent limbs (phocomelia).*

*Both mothers had taken a new drug (thalidomide) in early pregnancy. The doctor wishes to alert his colleagues worldwide to the possibility of drug related damage as quickly as possible (McBride, in the Lancet 1961). **Anyone who thinks ‘quick and dirty’ case reports are never scientifically justified should remember this example.*** ‘

And the source of this invaluable piece of advice? Dr. Trisha Greenhalgh, author of ‘How to Read a Paper’ (Greenhalgh, 2001).

## References

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