MSc Epidemiology 2010/11
Scientific Skills Course
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Critical appraisal of paper
Wakefield et al. 1998

1. Purpose and importance of the study
   a. Why was the study done?

      Description of a new syndrome (chronic enterocolitis and regressive developmental disorders) or description of a new syndrome in relationship to MMR vaccine (editor's opinion)

   b. What were the primary hypotheses and were they clearly stated?

      unclear and not stated

      The paper does not state a research hypothesis at all. Implicitly, the research hypothesis might be stated, "The administration of MMR vaccine to infants increases their risk of developing (a) a particular pattern of inflammatory damage in the gastro-intestinal tract and (b) autism or an autism-like syndrome." Introduction gives no reasoning at all for a hypothesis.

   c. Whom is the study about?

      12 children who had been referred to a paediatric gastroenterology clinic with both bowel symptoms (diarrhoea, abdominal pain, bloating, and food intolerance) and pervasive developmental disorder characterised by loss of skills that had been previously acquired. No clear case definition.

   d. Is the topic area relevant?

      Yes. In 1998, MMR vaccine had recently been introduced in the UK. Autism was discussed to rise in incidence. Questions were being asked about a possible link. A paper describing a study that explored this link would certainly have been appropriate to the Lancet and highly relevant to a general medical readership, so long as it was scientifically robust.

   e. Was the study original?

Yes. At the time, no previous study had explored in this way the link between MMR vaccine, bowel problems and autism in children.

2. Study design

a. What type of study was done?

'consecutive' case series of 12 children who had been referred to gastro department Various blood tests, gastrointestinal biopsies, and a sample of cerebrospinal fluid were taken from the children. The samples were examined to explore the extent of inflammatory reaction in the bowel and to exclude other diseases (such as thyroid disease, inherited metabolic syndromes and so on). Of dozens of tests done on each child, a number were abnormal, though no test was consistently abnormal in all the children. Eleven of the 12 children had microscopic evidence of inflammatory reaction in their bowel. The parents were asked to remember back and identify if and when MMR vaccine was given. In 8 of the 12 children, the onset of developmental delay was said to have occurred within 2 weeks of having the MMR vaccine, and in 3 it was said to have occurred within 48 hours.

b. Was this design the appropriate way to test the research hypothesis? Would another design be more appropriate?

No. If the hypothesis was that there is a *causal* link between MMR and autism-bowel syndrome, this study design was incapable of proving that link one way or the other.

The study had no comparsion group. We have no way of knowing that the unusual combination of bowel disease and autism-like syndrome might be equally frequent in children who had *not* received the MMR vaccine. When studying the possible harmful impact of a vaccine or environmental agent, it is standard scientific practice to include a comparison group of individuals who have not been exposed to the putative harmful agent (cohort study) or of individuals who are non-cases but coming from the same population from which the cases arise (case control study).

As autism is a rare disease one would perform a case control study.

A proper definition of exposition and outcome is lacking; entry criteria are not clearly stated.

The follow-up period during which the children were studied was short – days or weeks rather than months or years.

c. How was the size of the study population determined? Would another size be more appropriate?

The sample was extremely small. I would expect a scientific study claiming a causal association between two events (in this case, giving MMR vaccine and developing autism-bowel syndrome) to have a formal statistical calculation of the number of individuals that *ought* to be looked at. This is known as a power calculation. The reason why the Lancet does not normally publish studies on just 12 individuals (the usual number of research participants is several hundred, and not uncommonly, several thousand) is that the smaller the study, the more likely it is that an *apparent* causal link will turn out to be due to chance association.

d. Was assessment 'blind'?

The investigators were not 'blinded' – that is, the people who examined the children and analysed the specimens all knew that the children had received MMR vaccine and that a question had been raised about its link with autism-bowel syndrome. They would also have been aware that 'positive' findings would be highly likely to lead to a prestigious publication whereas 'negative' findings would not. In a scientifically robust study, the people who do the tests should be unaware of the status of the samples.

e. Was systematic bias avoided or minimised?

How likely is selection / information bias?

The sample was highly selected – that is, the authors deliberately picked out the tiny number of children who had been referred to a major specialist centre because they had *both* bowel symptoms *and* an autism-like syndrome. So the fact that these rare conditions occurred together proves nothing at all. The fact that children with diarrhoea or other chronic gastro-intestinal symptoms have microscopic evidence of inflamed bowels is also, in itself, unsurprising.

The alleged link with MMR vaccine was made on the basis of retrospective parental recall – in other words, parents (who had just signed a consent form to take part in a study of whether there is a link between MMR and autism) were asked to consider how closely in time the vaccine was with the onset of autism-like behaviour pattern in their child. Whilst there is no suggestion that parents deliberately fabricated the closeness of the link, the authors of the paper took no steps to guard against what is known as 'recall bias' (that is, remembering a closer association between two events

than actually occurred). The notion that a previously healthy child was 'normal' one day and showed clear signs of autism the next day is at odds with the clinical course of pervasive developmental disorder. Such syndromes tend to have a period of weeks or months during which the child's behaviour is causing some concern but is not clearly abnormal. Hence the firm statement of a "48 hour" or "2 week" interval between the administration of the vaccine and the diagnosis of autism is scientifically implausible and requires further explanation.

3. Analysis of the data

a. How was the association between exposition and outcome described? Was this adequate?

In absolute numbers. Number of children out of all children with syndrome who have had a MMR vaccine. No relative risk, no odds ratio.

This is not adequate.

b. How was chance accounted for in the association between exposure and outcome?

Chance was not accounted for, neither in the analysis nor in the discussion. No tests, no confidence intervals.

c. What was done to correct for confounding? Was this adequate?

Confounding was not considered.

4. Interpretation of results

a. Were study's conclusions supported by the data?

No. Whilst Wakefield and colleagues stated at one stage in their paper that their findings did not prove a causal link between MMR vaccine and autism-bowel syndrome ("We did not prove an association between measles, mumps, and rubella vaccines and the syndrome described"), the overall tone of the paper strongly suggests that they believed that they had demonstrated such a link.

b. How could bias have influenced the results of the study?

In many ways, see above.

e.g.:

- selection bias – 12 highly-selected patients referred to him (a group known to be interested in vaccines and adverse events, most came from one lawyer).

- recall bias – it is usually difficult to date precisely the onset of a syndrome like autism. Parents may attempt to relate its onset to an unusual event such as coincidental postvaccinal reaction.

c. For whom could the results be generalised?
No generalisation possible. Underlying population unclear. No controls.

d. Is the interpretation of the data conservative?
No. This is a case-series study, therefore no association / causation could be tested. It could have been useful to generate new hypothesis in order plan a new epidemiological study.

Adapted from http://briandeer.com/mmr/lancet-greenhalgh.html