ORIGINAL ARTICLE

No increased risk of relapse after meningococcal C conjugate vaccine in nephrotic syndrome

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Objectives: To investigate whether meningococcal C conjugate vaccine (MCCV) caused relapse in children with steroid-responsive nephrotic syndrome.
Design: A population-based study was conducted using an active surveillance system, developed to assess adverse events following vaccination, which linked hospital record information on relapses of nephrotic syndrome to community child health population MCCV data. An ecological study looking at hospital admissions for nephrotic syndrome in different age cohorts of children before and after the MCCV introductory campaign was also carried out.
Settings: South East England, and England and Wales.
Patients: 52 children having 162 relapses of nephrotic syndrome. Also, all hospital admissions of children aged 2–18 years with steroid-responsive nephrotic syndrome in England and Wales between 1995 and 2003, relating admissions to when MCCV was introduced in specific age cohorts.
Main outcome measures and analysis method: Self-controlled case series analysis looking for increased risk of relapse following MCCV and changes in admission rates for nephrotic syndrome (incidence ratio) following the introduction of MCCV to different age cohorts of children.
Results: There was no increased risk of relapse following MCCV in the self-control case series, where a relative incidence of 0.95 (95% confidence interval (CI) 0.61–1.47) was found in the 6-month post-vaccination period, or in the ecological study, which gave an incidence rate ratio of 1.05 (95% CI 0.95 to 1.15) for the quarter when MCCV was introduced and the following two quarters.
Conclusions: We found no association between MCCV and nephrotic syndrome, which is therefore not a contraindication to meningococcal vaccination.

There have been a few anecdotal reports implicating immunisation as a trigger for relapse of nephrotic syndrome in childhood.[1] In 2003, a specific increased risk for relapse was suggested after administration of meningococcal C conjugate vaccine (MCCV), based on a study of children with steroid-sensitive nephrotic syndrome attending a tertiary children's hospital.[2] A relative incidence of 1.84 (95% confidence interval (CI) 1.27 to 2.65) was reported for relapses in the 6-month post-vaccination period compared with 12 months pre-vaccination. While this study raised the possibility of an increased risk, it could not test the hypothesis because the assessed population contained the nine cases whose original relapses, apparently following MCCV administration, were the basis of the possible association. We have now independently tested the hypothesis.

Confirmation or refutation of an effect seemed particularly important, as following the *Lancet* publication,[2] the UK Committee on Safety of Medicines stated: ''In children with steroid-responsive nephrotic syndrome, Meningococcal C vaccination has been shown to be associated with a relapse of the condition within 6 months post-immunisation. The benefit of vaccination should be carefully weighed against the risk of relapse of nephrotic syndrome in any patient with a past history of the syndrome''.

We studied a geographical population, using an active surveillance system[3–6] which provides accurate dates of vaccination, together with case note review. We also undertook an ecological study, assessing quarterly hospital admissions for nephrotic syndrome before and after MCCV was introduced into different age cohorts during the campaign in 2000.

METHODS

Admissions to hospital of children aged from 1 to 17 years with nephrotic syndrome were identified from hospital episode data from North, East and South London, Essex, East Anglia, Sussex and Kent for the period 1 January 1999 to 31 December 2001 using established methods.[3–7] We excluded diagnostic labels suggesting non-minimal change causation; 319 children with likely steroid-responsive nephrotic syndrome were identified. These were linked where possible to population-based child health information system data and 119 children could be matched. In order to be able to detect a similar relative incidence to that seen in the tertiary hospital, power calculations indicated that at least 160 relapses were required (>80% power, 5% significance level to detect a relative incidence of 1.84).

Case note review of the matched admissions was undertaken, starting with those hospitals with most admissions, in order to confirm the diagnosis and identify all relapses in the study period. After reviewing 64 cases, 11 were identified as not having minimal-change nephrotic syndrome, leaving 53 children who had a total of 162 relapses; therefore further case note reviews were not undertaken. We used the same definition as Abeyagunawardena *et al*[2] for relapse (proteinuria, 3+ per 24 h, for three consecutive days), with separate relapses being at least 1 month apart to help ensure independence of relapse events. Of the 162 relapses, many (94) were not recorded in the

Abbreviations: CI, confidence interval; GOSH, Great Ormond Street Hospital; IRR, incidence rate ratio; MCCV, meningococcal C conjugate vaccine; MHRA, Medicines and Healthcare Products Regulatory Agency

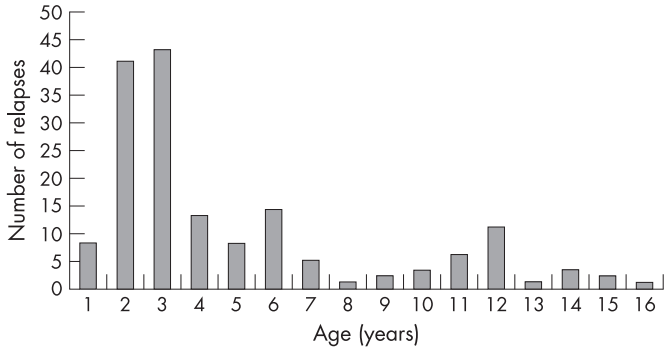

Figure 1 Age at relapse among 53 children with nephrotic syndrome.

hospital episode data, only in the case notes. In five relapses, where only the month was known, the 15th of the month was used as the onset of relapse. In none of these five episodes was MCCV given in the same or previous month. Twenty four of the children were female, 29 male, age range 1–16 years, mean age 4.9 years, relapses per child: 3, 13, 12, 4, 4, 4, 1, 0, 1, 0, 1 having from 1 to 11 relapses, respectively.

All children except one received one dose of MCCV during the study period. The child who received two had no relapses within 6 months of the second dose, so only the first was considered. The self-controlled case series method[7] was used to estimate the relative incidence of nephrotic syndrome within 1, 3 and 6 months of vaccination, with adjustment for age using the age groups 1, 2, 3, 4, 5/6, 7/8, 9/10 and 11+ years. A pre-vaccination period of 30 days was removed from the background by treating it as a separate risk period to allow for possible delayed vaccination following a relapse. Age at relapse is shown in fig 1.

We also performed an ecological analysis by examining total hospital admissions for nephrotic syndrome (ICD 10 codes NO40 and NO49) in England by quarter year (1995–2003), age (2–4, 5–8, 9–10, 11–14 and 15–18 years) and vaccine risk period (the risk period was the quarter(s) vaccine was delivered and the following two quarters; the no risk period was all other quarters). Age groups were selected to match the age cohorts targeted at different times while the vaccine was being introduced. The incidence rate ratio (IRR) for the vaccine risk period was estimated using negative binomial regression with separate quadratic time trends for each age group.

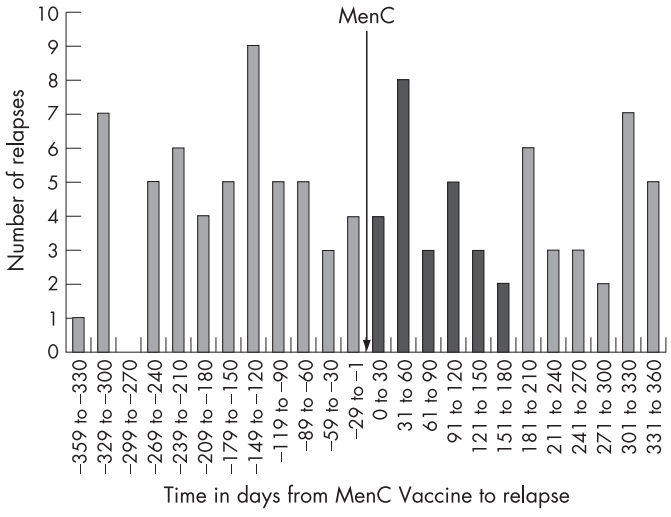

Figure 2 Numbers of relapses in 53 children with nephrotic syndrome in relation to when they received MCCV.

RESULTS

There were 53 children with nephrotic syndrome, with most relapses occurring in the second and third year of life (fig 1). In these 53 children, there were 25 relapses within 180 days of being vaccinated compared to 54 in the 360 days pre-vaccination, and 26 between 181 and 360 days post vaccination (fig 2). The other 57 relapses occurred outside these periods. Table 1 shows the estimate of relative incidence for various risk periods after vaccination, together with the relative incidence in the immediate pre-vaccination period. There was no evidence of an increased risk of nephrotic syndrome relapse in the 6 months after vaccination.

In the ecological study, which covered 36 quarters, there was an average of 356 admissions per quarter across all ages. In the year 2000, when MCCV was introduced and risk might be expected to be higher, there was an average of 385 admissions per quarter. When the data were analysed using the negative binomial model, no evidence of a temporary increase was found in admissions for nephrotic syndrome in the quarter-year of MCCV introduction or the following two quarters (IRR 1.05 with 95% CI 0.95 to 1.15).

DISCUSSION

We were unable to demonstrate any increased risk of relapse of steroid-sensitive nephrotic syndrome after vaccination with MCCV. This does not confirm an earlier report from Abeyagunawardena *et al*[2] which suggested a near doubled risk of relapse overall and a calculated risk of one relapse for every four doses of MCCV given to children with nephrotic syndrome.

The upper end of the 95% confidence CI in our study was 1.47, significantly below the point estimate of 1.84 from the Great Ormond Street Hospital (GOSH) study. This suggests that that study's findings may simply have been a chance observation in a single population. The GOSH study may also have been subject to bias through failure to independently collect clinical and vaccination data (a feature of our methods, where the review of case notes, in this case to classify relapse of nephrotic syndrome, was undertaken without knowledge of vaccination status and data were merged only for analysis). There was also a very low rate of MCCV uptake in the GOSH clinic population (less than 50%), whereas we only studied children with nephrotic syndrome who received MCCV during the study period.

Although our cases came from a general population, it is unlikely that there is a subgroup within a tertiary hospital population liable to react. Relapse rates were similar in the two populations, the study groups were comparably sized and similar analytic methods were used (by the same statistician). Both studies investigated children who received MCCV during the introduction of the vaccine which was associated with a catch-up campaign from November 1999, when all children over the age of 1 were offered a single dose of MCCV.

Our ecological analysis also showed no evidence of an association, supporting our main findings. However, the limitations of an ecological analysis mean that a true increased risk at an individual level would have been diluted due to lack

Table 1 Risk periods and relative incidence (RI) of relapse following MCCV in 53 children with nephrotic syndrome

Risk period (days)	RI (95% CI)	Cases
−30 to −1	0.94 (0.35 to 2.55)	4
0 to 30	0.90 (0.33 to 2.43)	4
0 to 60	1.14 (0.66 to 1.94)	15
0 to 180	0.95 (0.61 to 1.47)	25

of specificity of ICD coding and the fact that the vaccine risk quarters will not coincide exactly with individual level risk periods. As well, not all individuals were vaccinated and individuals might have been vaccinated outside the targeted time for their age group. To investigate this dilution effect further, we adjusted IRR to allow for 50% specificity of ICD coding and 40% capture of individual level vaccine risk in the vaccine-risk quarters. This gave an adjusted relative incidence of 1.25 with 95% CI 0.75 to 1.75. The confidence interval is now considerably wider but still does not contain the point estimate of 1.84 seen in the GOSH study.

There is no other supporting evidence for an association. There have been no reports of nephrotic syndrome following administration of other widely used similar conjugate vaccines such as Haemophilus influenza type b or pneumococcal, nor the conjugate quadravalent meningococcal vaccine (ACYW135) recently introduced in the USA. The UK Committee on Safety of Medicines Men C Working Group intensively monitored the safety of Men C vaccine during the initial immunisation campaign, with the Medicines and Healthcare Products Regulatory Agency (MHRA). Relapse of nephrotic syndrome was not identified as a potential safety concern (only two suspected cases were notified). Nor have there been cases which might suggest any association between MCCV and nephrotic syndrome reported from abroad to ADROIT (Adverse Drug Reactions Online Information Tracking, the MHRA database for storing suspected adverse drug reaction data).

Immune system mechanisms have been implicated in the initiation and relapses of nephrotic syndrome, with cytokines suggested as being involved in the onset of proteinuria. Abeyagunawardena *et al*[2] postulated that the meningococcal C capsular polysaccharide conjugated to a protein carrier molecule might have stimulated T cells so causing cytokine disturbance, but such a mechanism would be expected to be an acute process – it is biologically implausible to suggest such a mechanism would trigger a relapse months after vaccination.

Our results show the importance of case note review as a supplement to present routine data sets when linking information. They also confirm the need to replicate single reports which have suggested a problem when a new therapy is introduced, with robust systems like our active surveillance system, which has been developed to assess possible adverse events following vaccination and has proved capable of providing a rapid, reliable response to possible vaccine scares.[3–6 8 9]

The introduction of the Men C vaccine has proved a great success in reducing the burden of meningococcal serogroup C disease in the UK. It has been estimated that in 1999, before the vaccine was introduced, the total number of group C infections in England and Wales was about 1500 of which over 150 were fatal. There had been an overall reduction in cases of serogroup C disease of 81% by April 2001 related to Men C vaccines.[10]

The results of our study suggest that the Committee on Safety of Medicine's warning should be withdrawn; children with nephrotic syndrome can safely be given protection against Men C if required, without increased risk of relapse.

What is already known on this topic

- Various external agents, including vaccinations, have been incriminated anecdotally as triggering relapses of steroid-responsive nephrotic syndrome in children.
- A study from a tertiary children's hospital suggested that meningococcal C vaccine (MCCV) specifically might trigger relapses.
- This led to a warning from the UK Committee on Safety of Medicines that the vaccine might not be appropriate for children with nephrotic syndrome.

What this study adds

- We found no evidence that MCCV triggered relapses of nephrotic syndrome.
- MCCV can be safely recommended for children with nephrotic syndrome.
- Our active surveillance system provides an efficient and effective method to assess possible adverse events following vaccination.

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Competing interests: EM's department has received reimbursement for meningococcal C surveillance reports to vaccine manufacturers in accordance with the code of practice for the department (see http://www.hpa.org.uk/infections/about/dir/psp.pdf). There are no other conflicts of interest.

Ethics: The linked data adverse vaccination events programme has MREC and Patient Information Advisory Group approval.

Contributions of authors: EM, NA and BT designed the study, JS and LH-M identified the case notes and processed the data, BT assessed relapses, NA undertook the statistical analyses and all authors contributed to writing the paper.

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