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ARTICLE

Risk of Serious Neurologic Disease After Immunization of Young Children in Britain and Ireland

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ABSTRACT

OBJECTIVE. We sought to investigate the risk of serious neurologic disease after immunization in early childhood.

METHODS. The results of a 3-year prospective study of children (2–35 months old) in Britain and Ireland with encephalitis and/or severe illness with convulsions and fever were linked to each child's vaccine history. Cases were reported via the British Paediatric Surveillance Unit's network. The self-controlled case-series method was used to investigate associations between immunization and acute potential adverse events. The risk periods investigated were 0 to 3 and 0 to 7 days post–diphtheria, tetanus, whole cell pertussis, *Haemophilus influenzae* type b or meningococcal C conjugate vaccine and 6 to 11 and 15 to 35 days post–measles, mumps, rubella vaccine.

RESULTS. A total of 157 disease episodes from 155 children met the analytical case definition. There were 11 cases of herpes simplex encephalitis and 23 cases of primary human herpesvirus 6 and/or 7 infection. There was no evidence of a raised relative incidence of serious neurologic disease in any of the specified risk periods with the exception of a raised relative incidence of 5.68 in the 6–11 days after measles, mumps, rubella vaccine. Based on this relative incidence, between 3 and 6 of the 6 cases in this period were estimated to be attributable to the vaccine with a best estimate of 5. The 6 cases all had fever with convulsions lasting >30 minutes; in all but 1, there was complete recovery by discharge from hospital. Of the 5 patients who recovered, 1 had a concurrent primary human herpesvirus 6 infection and one a primary human herpesvirus 7.

CONCLUSIONS. Six to 11 days after measles, mumps, rubella vaccine there is an increased risk of fever and convulsions lasting >30 minutes. All 6 of the episodes temporally related to immunization met the criteria for complex febrile convulsions. The estimated attributable risk of serious neurological disease was similar to that previously found for measles vaccine.

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Key Words
encephalitis, febrile convulsions, status epilepticus, vaccine, HHV-6/HHV-7

Abbreviations
DTP— diphtheria, tetanus, whole cell pertussis
Hib—*Haemophilus influenzae* type b
MMR—measles, mumps, rubella
NCES—National Childhood Encephalopathy Study
HHV-6 — human herpesvirus 6
HHV-7— human herpesvirus 7
HPA—Health Protection Agency
MenC—meningococcal C conjugate
CSF— cerebrospinal fluid
RI—relative incidence
CI— confidence interval

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IMMUNIZATION IS A very effective health intervention.[1–5] As immunization-preventable infectious diseases and thus their serious clinical complications have become rare, more attention has necessarily been focused on vaccine-related adverse events.

Both diphtheria, tetanus, whole cell pertussis (DTP)/*Haemophilus influenzae* type b (Hib) and measles, mumps, rubella (MMR) vaccines can induce simple febrile convulsions in young children.[6–8] Such convulsions are common in childhood, usually with a benign outcome,[9,10] and there is good evidence that those occurring after MMR immunization do not increase the risk of subsequent epilepsy compared with febrile convulsions with other etiologies.[8] Nevertheless, there is some suggestion that very rare cases of more serious neurologic disease, such as encephalopathic illness, may be associated with this vaccine.[11] Although aseptic meningitis because of the Urabe strain of mumps in the MMR vaccine was reported, no such cases have been identified in the United Kingdom since this particular strain was removed from the vaccine.[12] If serious neurologic disease occurs after MMR immunization, it is most likely attributable to the measles component of the vaccine; indeed, the National Childhood Encephalopathy Study (NCES) conducted in the 1970s[13] reported an excess of cases after measles vaccine compared with controls.

A prospective survey of children in Britain and Ireland with serious neurologic disease, that is, encephalitis and/or severe illness with convulsions and fever, was recently conducted to assess the contribution of human herpesvirus 6 (HHV-6) and 7 (HHV-7) to the burden of such illness.[14] Because the data collected included each child's vaccine history, we were able to use the self-controlled case-series method[15] to investigate whether there was an increased risk of vaccine-related adverse events after immunization. The MMR vaccine is given at ~13 months of age, which coincides with the age when status epilepticus with fever attributable to primary HHV-6 and HHV-7 infections is most likely to occur.[14] Therefore, we were especially interested to determine the contribution of these viruses to morbidity after MMR immunization.

METHODS

Patients

Case Ascertainment

The survey used the monthly surveillance card distributed by the British Paediatric Surveillance Unit to all consultant pediatricians in Britain and Ireland; reporting rate at the time was 92.7%.[15] Each month between October 1998 and September 2001, pediatricians were requested to report all children 2 to 35 months old with suspected encephalitis and/or severe illness with fever and convulsions.[15] Details of each child's neurologic illness were collected from the reporting pediatrician by using a short standard questionnaire; we also asked whether at the time of discharge the child had fully recovered from the episode of disease. Each questionnaire was scrutinized by a physician (Dr Ward) to determine whether the details fitted the case definition (see Table 1); difficult cases were referred to ≥1 pediatrician (Drs Ohrling, Verity, and Ross) for a final decision.

TABLE 1 Definitions of Terms Used

Onset of illness: day of hospital admission
Fever: temperature of ≥37.5°C; the questionnaire asked whether there was a fever and also for the maximum temperature recorded at any site by any method
Encephalopathy: a depressed or altered level of consciousness
Case definition of serious neurologic disease: any child 2–35 mo old with a severe illness with fever and convulsions (a) and/or encephalitis (b) was included
(a) Severe illness with fever and convulsions
(i) with a total duration of >30 min; or
(ii) followed by encephalopathy for 2–23 h; or
(iii) followed by paralysis or other neurologic signs not previously present for ≥24 h
(b) Encephalitis (adapted from Kolski et al[16]).
(i) Encephalopathy for ≥24 h and ≥2 of the following: fever, convulsions, focal neurologic findings (≥24 h), pleocytosis (>5 leukocytes per μL CSF), characteristic abnormal results of neuroimaging (computerized tomography or MRI), herpes simplex virus nucleic acid (or nucleic acid of any other virus proven to cause encephalitis) in CSF; or
(ii) postmortem histologic evidence of encephalitis
(c) Exclude
(i) viral (aseptic) meningitis without encephalopathy
(ii) the following confirmed causes were excluded: hypoxic/ischemic; vascular; toxic; metabolic, neoplastic, traumatic, and pyogenic infections
(iii) uncomplicated convulsions or a series of convulsions lasting <30 min
(iv) immunocompromised children

Note that in this article, the term "convulsion" is used synonymously with "seizure." Primary HHV-6 and HHV-7 infections were defined by using authenticated tests,[17–19] that is, viral antibody and DNA tests, to detect antibody seroconversion and DNAemia.[14]

Immunization History

For those cases that met the case definition, the immunization history was obtained from the child's general practitioner by the Immunization Department, Health Protection Agency (HPA), Centre for Infections, London. The history was sought sufficiently long after the event so that immunizations given up to 1 year later were included.

Immunization Schedules for Early Childhood

Britain

At the start of our survey in 1998, the schedule comprised a primary course of DTP/Hib vaccine together with oral polio vaccine at 2, 3, and 4 months of age, followed by MMR vaccine at 12 to 15 months of age. In November 1999, a primary course of the meningococcal C conjugate (MenC) vaccine was introduced for children 2, 3, and 4 months of age, with a catch-up program for older children.[5]

Republic of Ireland

The schedule differed slightly from that in Britain: diphtheria-tetanus-acellular pertussis, Hib, and oral polio vaccines were given at 2, 4, and 6 months of age and MMR at 12 to 15 months of age. In October 2000, a primary course of MenC vaccine was introduced for children 2, 4, and 6 months of age, with a catch-up program for older children.

Statistical Analysis

Cases

All episodes of illness that met the case definition (see above) and for which there was a sufficient vaccine history were included in the analysis. A second episode of illness was included as a case if the child was readmitted to hospital more than a month after the first. Cases were stratified into those children aged 2 to 11 months for assessment of the risk from DTP/Hib and MenC vaccines and those aged 12 to 35 months for MenC vaccine, given in the catch-up campaign, and MMR vaccine. MMR vaccine data were not required for patients presenting in the first year of life, and DTP/Hib vaccine data were not required for those presenting in the second and third year of life.

Immunization Risk Periods

The periods in which fever and convulsions attributable to the vaccine in question might be expected were 0 to 3 and 0 to 7 days for MenC and DTP[5,20] and for MMR 6 to 11 days.[6] Similarly 15 to 35 days after MMR vaccine was considered a risk period for encephalitis because this is the incubation period for postinfectious encephalitis induced by wild-type measles[21] and for aseptic meningitis induced by the Urabe vaccine strain of mumps.[22]

Self-Controlled Case-Series Method

This statistical method[23] uses data on cases only.[6] In the present study, data on episodes, that is, cases of serious neurologic disease, in children between 2 to 35 months of age (61–1094 days of age), and data on immunization history were collected over a defined calendar time period. The resulting data set consisted of the dates of disease episodes and of vaccine administration. By using these data for each individual, each day of age could then be assigned as falling into a particular immunization risk period or outside it, such as in the control period. Similarly, each disease episode (event) fell into either a risk or control period. This enabled us to calculate person time and events within and outside the risk periods for each individual, hence the relative incidence in the immunization risk period compared with the control period. The effect of age was adjusted for by fitting it as a factor in the self-controlled case-series analysis; for the 2- to 11-month-old group, 10 sequential periods of 1 month were used, and for the 12- to 35-month-old group, 12 sequential periods of 2 months were used. For the older children, the analysis was also applied according to whether or not there was coincident primary HHV-6 and/or HHV-7 infection.

Ethics Approval

This was given by the Public Health Laboratory Service Ethics Committee, London.

RESULTS

Number of Cases

Of the 267 episodes of serious neurologic disease reported, 163 met the case definition. Because in 6 instances there was an incomplete vaccination history, only 157 cases were analyzed. These cases came from 155 children, 8 of whom were from the Republic of Ireland and 147 from Britain; 1 child had an admission aged under 1 year and another episode of neurologic disease when >1 year old, and a second child had 2 episodes when >1 year old. Fifty cases were in children aged 2 to 11 months, and 107 were in children 12 to 35 months old.

Clinical Findings

Etiology

In ~90% of the cases of serious neurologic disease, serum was available[15] and was tested for primary HHV-6 and HHV-7 infection, regardless of the time from immunization; in 23 cases, the illness was directly attributable to primary HHV-6 or HHV-7 infection,[14] that is, 7 children <1 year old and 16 from the older group. There were 9 cases (18%) of herpes simplex encephalitis in the first year of life, and 2 (2%) in the second. No cases of pertussis, measles, mumps, or rubella were reported.

Short-term Outcome

Two children were dead on presentation, and an additional child died within 1 month; in none of the 3 was either herpes simplex encephalitis or primary HHV-6 or HHV-7 infection identified. Twenty-nine (58%) of all cases in children 2 to 11 months old were reported to have recovered at the time of discharge compared with 80 (75%) of the older children ($P = .04$, Fisher's exact test).

Clinical Features

Eighty-three children presented with symptoms including encephalopathy at ≥24 hours. Fever was reported in 149 patients and in 135, the maximum temperature was specified (mean: 38.8°C; range: 37.5–41). Convulsions with fever were reported in 139 patients (120 were in previously neurologically normal children); of the 139, 94 (68%) had seizures lasting >30 minutes, 65 (47%) had encephalopathy lasting ≥24 hours, and in 113 a cerebrospinal fluid (CSF) sample was taken (33 samples showed pleocytosis, that is, inflammatory cells indicating central nervous system infection). Figure 1 shows the age distribution of all 139 patients with fever and convulsions and compares the patients with CSF pleocytosis, with the remaining 106 patients, 76 of whom had convulsions lasting >30 minutes and 14 convulsions for 15 to 30 minutes. The peak incidence of the 106 cases was in the second year of life. Fifty-two percent (17 of 33) of patients with CSF pleocytosis were reported to have recovered at the time of discharge compared with 79% (84 of 106) of the remaining patients ($P = .003$, Fisher's exact test).

Immunizations and Sequelae

Forty-seven (94%) of 50 children <1 year old received 3 doses of DTP/Hib vaccine; of the 3 who had <3 doses, 1 had a single dose and 2 had 2 doses. MMR vaccine uptake in those >1 year old was 96 (90.6%) of 106. For the MenC vaccine, it was not possible to estimate coverage because this was introduced into the immunization program during the course of the study; of the children <1 year old, 12 received 3 doses of MenC and 2 had 2 doses, and of the older children, 49 had a single dose of MenC.

Table 2 shows the estimated relative incidence of serious neurologic disease in the various specified postimmunization periods for DTP/Hib, MenC, and MMR vaccines. There is no evidence of a raised relative

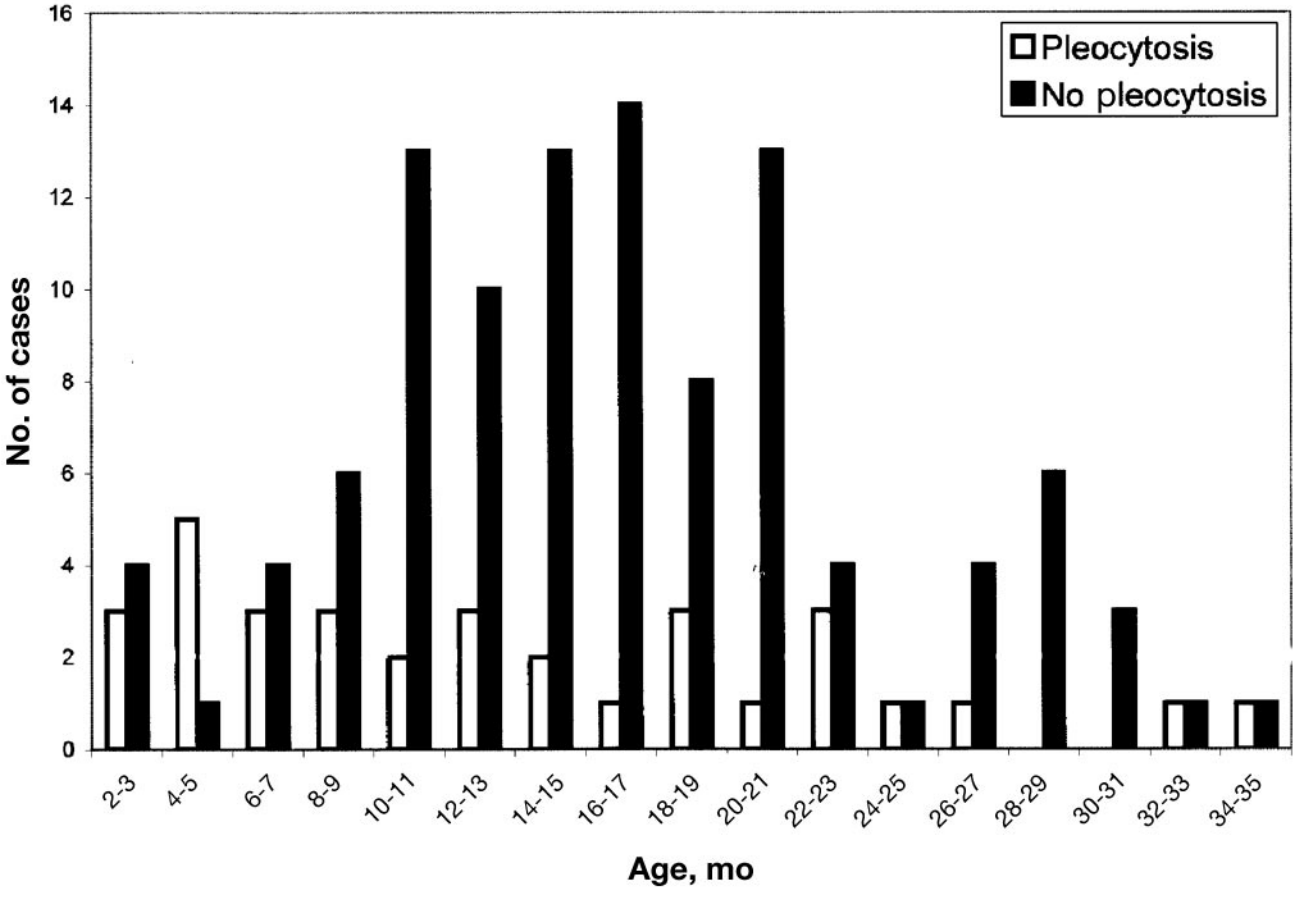

FIGURE 1
Age distribution of the 139 confirmed patients with symptoms of both fever and convulsions: comparison of those with CSF pleocytosis with the remaining cases.

TABLE 2 **Relative Incidence of Severe Neurologic Disease in Various Specified Postimmunization Risk Periods**

Age and Vaccine Given	Risk Period Days	No. of Cases in Period	Relative Incidence (95% CI)
2–11 mo			
DTP/Hib	0–3	0	0.00 (0.00–1.92)
	0–7	2	0.97 (0.22–4.30)
MenC	0–3	0	0.00 (0.00–25.5)
	0–7	0	0.00 (0.00–1.70)
12–35 mo			
MMR	6–11	6	5.68 (2.31–13.97)
	15–35	5	1.34 (0.52–3.47)
MenC	0–3	0	0.00 (0.00–7.92)
	0–7	1	1.28 (0.17–9.75)

incidence for DTP/Hib and MenC vaccines or for MMR vaccine in the 15- to 35-day risk period. However, the relative incidence (RI) 6 to 11 days after MMR vaccine was raised at 5.68; the fraction of cases (RI − 1/RI) attributable to vaccine was 82% (95% confidence interval [CI]: 57%–93%), that is, between 3 and 6 of the 6 cases observed with a best estimate of 5. Because all of the vaccine-associated cases occurred in British children, we can estimate the vaccine-attributable risk of serious neurologic disease after the first dose of MMR vaccine as 1 in 365 000 doses (95% CI: 1 in 1460 000 to 1 in 140 000). This is based on data for the study period: a 1-year-old population of 2.1 million (National Statistics Office Web site; www.statistics.gov.uk/popest) and with overall vaccine coverage at 87% (HPA Web site; www.hpa.org.uk/cdr/archives).

Table 3 shows the clinical details of the 6 children whose illness occurred 6 to 11 days after MMR immunization. One child had concurrent primary HHV-7 infection and 1 a primary HHV-6 infection. Three children were ventilated because of seizures, and 1 of these had not recovered fully at the time of discharge.

Table 4 compares the risk of serious neurologic disease after MMR vaccine in the presence or absence of primary HHV-6 or HHV-7 infections and shows that the relative incidences are similar.

DISCUSSION

In this analysis, we linked the results of a 3-year prospective survey of children with serious neurologic disease, that is, encephalitis and/or severe illness with fever and convulsions, to each child's vaccine history to determine the risk of adverse events associated with immunization. The primary aim of the survey was to investigate the relationship between HHV-6 or HHV-7 infections and neurologic illness.[14] No mention was made in the reporting instructions for pediatricians of the secondary aim of linkage with vaccine histories as described above, thus excluding any bias toward immunization. The coverages for DTP/Hib and MMR vaccines were 95.9% and 90.6%, respectively, which is similar to vaccine coverage data for 1998 to 2001 (HPA Web site, www.hpa.org.uk/cdr/archives).

The majority of our patients had convulsions with fever (in more than half, the seizures lasted >30 minutes), most recovered fully, and in about three quarters of patients, there was no evidence of inflammatory cells in the CSF, all of which is suggestive of febrile convulsions rather than encephalitis. Indeed, 23 of our patients, a significant proportion, had primary HHV-6 or HHV-7 infection, both of which are well-established causes of febrile convulsions.[24,25] Moreover, the peak incidence of our cases without CSF pleocytosis was in the second year of life, with an age distribution (Fig 1) the same as that of febrile convulsions, which occur mainly between the ages of 6 months and 3 years, peaking at around 18 months.[26]

Febrile convulsions may be simple or complex and are defined as "An epileptic seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures."[27] Between 2% and 4% of all children in Europe and the United States experience ≥1 convulsion associated with a febrile illness before the age of 5 years. Of children who have febrile convulsions, 25% have complex febrile convulsions (as opposed to less severe or simple febrile convulsions); these have ≥1 of the following characteristics: >15 minutes duration, >1 convulsion in 24 hours, or a convulsion with focal features.[28]

Thus, many of our patients met the criteria for complex febrile convulsions and fell within our definition of severe illness with fever and convulsions rather than that of encephalitis. This impression is confirmed by a recent report that about half of the episodes of status epilepticus in previously neurologically normal British children 0 to 4 years old were in fact complex febrile convulsions lasting ≥30 minutes.[29] Nevertheless, it may be impossible in an ill child with fever and convulsions to exclude viral encephalitis, even if there are no inflammatory cells in the CSF. This distinction was especially difficult for the children with primary HHV-6 or HHV-7 infections in whom viral DNA is sometimes detected by polymerase chain reaction in the CSF,[24,25] despite a clinical diagnosis of febrile convulsions and where recovery is the norm. An additional difficulty in excluding encephalitis was encountered because the management of complex febrile convulsions may include drug therapy and sedation for ventilation, both of which may result in a depressed level of consciousness without there being underlying intracerebral pathology. It was therefore decided to include all our cases in the single category of serious neurologic disease.

As regards MMR vaccine, we found no evidence of a raised relative incidence of serious neurologic disease 15 to 35 days after immunization. In contrast, we identified

TABLE 3 **Clinical Details of Patients Whose Neurologic Disease Occurred 6 to 11 Days After MMR Vaccination**

Patient No.	Vaccine Type	Onset of Illness: Days After Immunization	Rash[a]	Fever (Maximum Temperature), °C	Convulsions >30 min/ Type of Convulsion	Ventilated and Sedated for Control of Convulsions	Encephalopathy	CSF Pleocytosis	Confirmed Concurrent Infection	Days in Hospital/ Recovery?
1[b]	MMR/MenC1	8	No	39	Yes/whole body	Yes	≥24 h	No	Primary HHV-7	5/yes
2[c]	MMR	7	Yes	40	Yes/whole body	Yes	≥24 h	No	None	20/no[d]
3[c]	MMR	11	No	38	Yes/whole body	Yes	2–23 h	No	None	13/yes
4[c]	MMR/MenC1	7	No	38.5	Yes/whole body	No	2–23 h	No	None	4/yes
5[c]	MMR/MenC1	11	Yes	40	Yes/focal[e]	No	No	ND	None	3/yes
6[c]	MMR	7	Yes	39.8	Yes/whole body	No	No	No	Primary HHV-6	3/yes

ND indicates not done (ie, CSF not taken).

[a] Maculopapular.

[b] Previous infantile spasms.

[c] Previously neurologically normal. No previous convulsions.

[d] Not fully recovered at time of discharge. No additional convulsions or cerebral palsy but severe cognitive problems.

[e] Followed by Todd's paresis.

TABLE 4 **Relative Incidence of Severe Neurologic Disease in Specified Prevaccination and Postvaccination Risk Periods for MMR Vaccine: Comparison in the Presence or Absence of Concurrent Primary HHV-6 or HHV-7 Infection**

Concurrent Primary HHV-6 or HHV-7 Infection	Risk Period Days	No. of Cases in Period	Relative Incidence (95% CI)
No	6–11	4	5.80 (1.98–16.99)
	15–35	4	1.52 (0.52–4.41)
Yes	6–11	2	5.55 (1.12–27.63)
	15–35	1	0.86 (0.10–7.23)

6 cases that arose 6 to 11 days after MMR vaccine; all had convulsions for >30 minutes with fever and all met the criteria for complex febrile convulsions. The raised relative incidence of serious neurologic disease in this period was 5.68 above background which is similar to the previous estimates of 2 to 4 times background for the more common simple rather than complex febrile convulsions.[6–8,12] Five (95% CI: 3–6) of 6 cases observed were estimated as attributable to MMR vaccine. Three children received MenC vaccine at the same time, but there is no reason to suppose that this latter vaccine contributed to the illness because the expected time course of reactions to MenC vaccine would be earlier, that is, maximal within the first 3 days.[5] Two of 6 patients had coincident infections, a primary HHV-6 and a primary HHV-7, both of which are common causes of febrile convulsions and are known to increase the risk of severe illness with fever and convulsions in young children by 7- to 10-fold, especially at the age when MMR vaccine is given.[14] Five of 6 children, including the 2 with primary HHV-6 or HHV-7 infection, were reported as recovered on discharge from hospital, but the child who had the longest inpatient stay was not fully recovered at this time. The natural history of febrile convulsions is generally benign,[9,10] even if the convulsions last >30 minutes[30,31] and perhaps, therefore, this child had some other explanation for its illness. The data available to us do not allow us to conclude whether or not there was a causal relationship between MMR immunization and the outcome in this child who did not recover by the time of discharge from hospital.

Our case definition was derived from that of the NCES, a prospective study of children 2 to 35 months old in England, Scotland, and Wales from 1976 to 1979,[13] but which encompassed a narrower spectrum of disease. Thus, the NCES case definition included severe illness with fever and convulsions and encephalitis but also encephalopathy, epilepsy, Reye's syndrome, and infantile spasms. In both our survey and that of the NCES, acceptance of the case definition was based on the history and physical examination as recorded on a short standard questionnaire. Approximately 60% of the NCES patients had encephalitis and/or severe illness

with fever and convulsions[13] and as with our patients, over half of this subset consisted of complex febrile convulsions. The NCES reported a relative risk of serious neurologic illness of 3.9 in previously neurologically normal children admitted to the hospital 7 to 14 days after measles vaccine, all of whom fell within the definition of encephalitis and/or severe illness with fever and convulsions and notably had a normal outcome in both the short[13] and longer term.[32] In our survey, we observed a raised relative incidence of 5.68 of serious neurologic disease in children admitted to hospital 6 to 11 days after MMR vaccine, all of whom had fever with convulsions >30 minutes. Therefore, the outcome of the 2 studies was very similar and, although the difference between the 2 relative incidences is not significant, our slightly higher value may reflect the greater specificity of our case definition for vaccine-attributable events.

It seems likely that the number of cases we collected in the 3 years of our survey was an underestimate because many more cases of encephalitis and/or fever with convulsions were accrued by the NCES in the same length of time.[13] Measles, mumps, rubella, and pertussis were common childhood illnesses when the NCES was conducted but have almost disappeared from Western countries in the last 20 years because of effective immunization programs resulting, as reported from Finland, in fewer cases of encephalitis.[33] However, this change does not explain the discrepancy between the NCES and our survey; even when the above infectious diseases are excluded from the NCES data, there remain ~3.3 times more cases. Furthermore, this impression is confirmed on analysis of Hospital Episode statistics for England from 1998 to 2001, because the number of children aged 1 to 35 months admitted to hospital with encephalopathy/encephalitis from 1998 to 2001 is ~2.9 times more than the number we identified (data not shown). This threefold underascertainment of cases means that our estimated attributable risk of serious neurologic disease of 1 in 365 000 doses of MMR vaccine is in fact closer to 1 in 100 000, similar to the NCES value of 1 in 87 000 doses of measles vaccine.

Others have investigated the relationship between MMR vaccine and encephalitis or encephalopathy by using large linkage databases. A record-linkage study in Finland[34] of over half a million children aged between 1 and 7 years found no evidence of a risk of developing encephalitis compared with background rates. The risk period investigated was broad being within 3 months of MMR vaccine. More recently, a retrospective case-control study of encephalopathy using health maintenance organizations found an odds ratio of 0.40 within 7 to 14 days of MMR vaccine for cases compared with controls.[35] This lack of identification of adverse events contrasts with the findings of our survey and that of the NCES. The difference probably results from the inclusion not only of encephalitis/encephalopathy but also severe illness with fever and convulsions consisting mainly of complex febrile convulsions in both the present survey and the NCES.

Finally, it should be noted that we found no evidence of an increased relative incidence of serious neurologic disease with DTP/Hib vaccination given at 2, 3, and 4 months of age. This differs from the findings of the NCES, set up in response to concerns about pertussis vaccine and neurologic disease and which reported a relative risk of 3.0 within 3 days of DTP vaccine. At the time of the NCES, the DTP vaccine schedule was 3, 5, and 10 months. Farrington et al[6] found a raised relative incidence for convulsions limited to the third dose of DTP vaccine. During the course of their study, the timing of DTP immunization was changed in 1990 to an accelerated schedule at 2, 3, and 4 months, and comparison with the previously used schedule showed a fourfold decrease in febrile convulsions. On the basis of this observation, the authors[6] suggested that the raised incidence after the third dose of DTP vaccine was probably because of immunization at the late age of 10 months and that the risk of a simple febrile convulsion would be remote if the DTP vaccine schedule was completed by 4 months; our findings confirm this for complex febrile convulsions.

CONCLUSIONS

We have investigated the risk of severe neurologic disease after immunization by relating the results of a prospective survey of such illness to the patient's vaccine history. There was no evidence of a risk after DTP/Hib or MenC vaccines or 15 to 35 days after MMR vaccine. However, 6 to 11 days after MMR vaccine, we identified a raised relative incidence of adverse events because of children having attacks meeting the criteria for complex febrile convulsions. Our findings are comparable to those of the NCES; in that study, the estimated attributable risk of serious neurologic disease for measles vaccine was similar to that found by us for MMR vaccine.

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