A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines

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Summary

We describe a new method for active post-marketing surveillance of vaccine safety based on patient records. We studied the association between diphtheria/tetanus/pertussis (DTP) vaccination and febrile convulsion, and between measles/mumps/rubella (MMR) vaccination and febrile convulsion and idiopathic thrombocytopenic purpura (ITP) in five district health authorities in England by linking vaccination records with computerised hospital admission records.

We found an increased relative incidence for convulsions 0–3 days after DTP vaccination. The effect was limited to the third dose of vaccine for which the attributable risk (all ages) was 1 in 12 500 doses. Completion of vaccination by 4 months instead of 10 months after the change in the UK to an accelerated immunisation schedule may have resulted in a 4-fold decrease in febrile convulsions attributable to DTP vaccine. 67% of admissions for a convulsion 6–11 days after MMR vaccination were attributable to the measles component of the vaccine (risk 1 in 3000 doses). An excess of admissions for a convulsion 15–35 days after MMR vaccination was found only for vaccines containing the Urabe mumps strain (1 in 2600 Urabe doses). There was a causal association between MMR vaccination and ITP resulting in admission 15–35 days subsequently; there was no evidence of a mumps strain-specific effect. The estimated absolute risk of 1 in 24 000 doses was 5 times that calculated from cases passively reported by clinicians. This finding emphasises the need for active surveillance of adverse events.

The record linkage method that we used is an effective way to identify vaccine-attributable adverse events.

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Introduction

In most countries vaccine safety relies on passive reporting of adverse vaccine reactions by clinicians and under-reporting is inevitable. Thus in 1993[1] we described the failure of passive surveillance in the UK to detect an unacceptably high risk of aseptic meningitis with measles/mumps/rubella (MMR) vaccines that contained the Urabe mumps strain. The Jeryl Lynn strain is now the only mumps vaccine used in the UK. In addition, passive reports cannot be used to establish causal relations for events, such as convulsions, that can occur in the absence of vaccination. With the recent introduction of *Haemophilus influenzae* b (Hib) vaccines, and the probable introduction of acellular pertussis vaccines in the near future, there is an urgent need to find more reliable methods of adverse event surveillance.

We report the results of a new epidemiological and statistical method based on the linkage of routinely available computerised hospital admission records with vaccination records. We used this active surveillance method to assess the attributable risk of a convulsion after diphtheria/tetanus/pertussis (DTP) and MMR vaccines and to investigate the relation between MMR vaccine and idiopathic thrombocytopenic purpura (ITP) in children under 2 years in five districts in England.

Subjects and methods

We identified children aged 29–730 days who had been discharged from hospital with a diagnosis of febrile convulsion (International Classification of Disease [ICD] code 780.3), and children aged between 366 and 730 days who had been discharged with a diagnosis of meningitis categorised as mumps, aseptic, or viral (072.1, 047., 321.), or ITP (287.3) from computerised hospital records in five districts in England (Ashford, Leicester, Nottingham, Preston, and Chorley & Ribble) for varying periods between October, 1988, and February, 1993. Re-admissions within 72 h with the same diagnosis were counted as one episode. We obtained dates of vaccination and batch numbers of MMR vaccines from computerised child health and general practice records.

For each type of clinical event, we calculated the relative incidence (RI) in specified post-vaccination risk periods compared with a control period by Poisson regression conditional on the number of admissions for each case.[2] The risk periods for MMR vaccine (6–11 and 15–35 days after vaccination) were those in which neurological events attributable to the measles and mumps components might be expected.[1] The risk periods for DTP vaccine (0–3, 4–7, and 8–14 days) were based on the results of the National Childhood Encephalopathy Study.[3] The control period for each vaccine was defined as the time not included in a risk period. Only infants aged less than 1 year who had had at least 1 dose of DTP vaccine and with any subsequent doses separated by at least 21 days, or children 12–24 months old

Dose	Age ≤28 wks		Age >28 wks		All ages	
	Number of admissions	RI (95% CI)	Number of admissions	RI (95% CI)	RI (95% CI)	p value
1st or 2nd vaccine dose	5	1·3 (0·5–3·2)	1	0·8 (0·1–5·5)	1·2 (0·5–2·6)	0·70
3rd vaccine dose	3	2·7 (0·8–8·6)	8	3·1 (1·5–6·4)	3·0 (1·6–5·5)	<0·001

Table 1: **Admissions for a febrile convulsion 0–3 days after DTP vaccination**

with an MMR vaccination record, were included in the RI analyses for each vaccine. The analyses were adjusted for age and were grouped in six equal intervals of about 2 months.

Absolute risks were calculated as the number of cases divided by total number of doses given in the catchment areas of the hospitals during the study, estimated from COVER data[4] and health authority records. For RIs above 1, the attributable risk was calculated similarly with the excess number of cases as numerator. All risks after Urabe or Jeryl-Lynn MMR vaccines were adjusted for missing batch information.

Results

DTP vaccination

595 children under 1 year were admitted with a febrile convulsion, the number admitted increasing sharply after 6 months of age. DTP vaccination records were obtained for 443 (74%) children, the proportion varying between districts from 69% in Nottingham to 81% in Ashford. These 443 children had 491 admissions for convulsions between 1–12 months of age of which 17 occurred within 0–3 days, 5 within 4–7 days, and 21 within 8–14 days of receiving DTP vaccine. Of the 17 cases that occurred within 3 days of vaccine, 11 (65%) occurred after the third dose. An RI significantly greater than 1 was found only in the 0–3 day post-vaccination period (RI 1·9, 95% CI 1·2–3·2, p=0·009). This effect was seen only after the third dose and was independent of age (table 1).

During the relevant periods, an estimated 91 000 primary courses of DTP vaccine were completed. The absolute risk of a febrile convulsion 0–3 days after any dose was 17/(3×91 000) or 1 in 16 000 doses. For third doses the absolute risk was 11/91 000 or 1 in 8500 doses. 7 of the 11 cases that occurred within 3 days of the third dose were estimated to be caused by vaccination (attributable risk 1 in 12 500). To comply with national policy, the immunisation schedule was changed in the districts during the study from 3, 5, and 10 months to 2, 3, and 4 months. Because there was no precise information on implementation, we could not calculate reliable attributable risk estimates under the old and new schedules. However, the absolute risk of admission was 4 times higher in 10-month-old infants than in 4-month-old infants after adjusting for vaccine effects.

MMR vaccination

There were 1451 admissions in 1285 children aged 12–24 months in one of the three diagnostic categories. We obtained MMR vaccination histories for 966 (75%) children, and there were similar variations between districts as for DTP vaccine. Of these 966 children, 752 (78%) had a batch number recorded. Among the linked admissions, there were 1057 for febrile convulsions (2 also coded as aseptic meningitis) and a further 5 for aseptic meningitis alone. These 1062 admissions occurred in 952 children. 16 episodes of ITP occurred in 14 children (table 2).

There was a significantly increased RI for febrile convulsions 6–11 days after vaccination for Jeryl Lynn and Urabe vaccines (p<0·001 for each vaccine, RI 3·77, 95% CI 1·95–7·30 and 2·70, 1·81–4·01, respectively), but only for Urabe vaccines in the 15–35 day period (Urabe 1·66, 1·26–2·20, p<0·001; Jeryl Lynn 1·04, 0·56–1·93, NS). Significantly increased RIs were also found for admissions for ITP and aseptic meningitis 15–35 days after vaccination, the latter being restricted to Urabe vaccines. The 4 vaccine-associated cases of ITP were in different children with onset 19, 21, 22, and 34 days after vaccination. Of the 2 cases for which there was batch information, 1 occurred after Jeryl Lynn and 1 after Urabe-containing vaccine.

We estimated that 97 300 doses of MMR vaccine were given during the study period, of which 77 200 contained the Urabe mumps strain and 20 100 the Jeryl Lynn strain. Table 3 shows the estimated absolute and attributable risks of events after MMR vaccination.

Discussion

Our active surveillance methods confirmed a significant association between DTP vaccination and febrile convulsion resulting in hospital admission in infants less than a year old. The vaccine effect appears to be limited

Event	Number of admissions	Admission 6–11 days after vaccination			Admission 15–35 days after vaccination		
		No	RI* (95% CI)	p value	No	RI* (95% CI)	p value
Febrile convulsion or aseptic meningitis	1062	49	3·04 (2·27–4·07)	<0·0001	85	1·51 (1·21–1·90)	<0·001
Aseptic meningitis alone	7	0	..	..	5	38·1 (4·30–336)	0·001
Idiopathic thrombocytopenic purpura	16	0	..	..	4	6·44 (1·94–21·4)	0·002

*RI=relative incidence.

Table 2: **Admissions after MMR vaccination according to clinical event**

Event: days after vaccination	Type of MMR vaccine	Number of cases	Absolute risk	Events attributable to vaccine (%)	Attributable risk
Febrile convulsion: 6–11 days	Any	49	1:2000	33 (67)	1:3000
Febrile convulsion or aseptic meningitis: 15–35 days*	Urabe	57	1:1100	23 (40)	1:2600
Febrile convulsion: 15–35 days*	Jeryl Lynn	9	1:1700	0	..
Aseptic meningitis: 15–35 days	Urabe	5	1:15000	5 (97)	1:16000
Idiopathic thrombocytopenic purpura: 15–35 days	Any	4	1:24000	3 (84)	1:29000

*Risk estimate adjusted for missing batch information on 19 of the 85 cases.

Table 3: **Risk events after MMR vaccination in 12–24-month-old children**

to the third dose and caused two-thirds of the admissions for febrile convulsions that occurred within 3 days of this dose (attributable risk 1 in 12 500). The time period and magnitude of the increased risk after vaccination was consistent with that observed in the National Childhood Encephalopathy study which looked at more severe neurological events.[3]

Although we did not have sufficient data to estimate schedule-specific risks, the 4-fold difference in the absolute risk of febrile convulsion between 4 and 10 months, together with a constant multiplicative vaccine effect, indicates a probable 4-fold reduction in cases attributable to DTP vaccination following the change from a 3, 5, 10 month to a 2, 3, 4 month schedule. Compared with the 1 in 3000 risk of admission for a convulsion due to the measles component 6–11 days after MMR vaccine, the risk of a convulsion after whole-cell DTP vaccine under the accelerated schedule is remote. However, as more antigens come to be given at the same time as DTP vaccine, the rate of such adverse events may increase. Therefore we will repeat the study in cohorts who are given Hib and DTP vaccine simultaneously. Our method will also be used to assess acellular DTP vaccines if these replace whole-cell vaccines.

Our study showed that there was an attributable risk of 1 in 2600 doses of a febrile convulsion 15–35 days after giving Urabe MMR vaccine. There was no excess of admissions in the same period when Jeryl-Lynn vaccine was given. We feel that these results refute the claim[5,6] that the lymphocytic cerebrospinal fluid caused by Urabe vaccine does not lead to neurological symptoms but is simply a chance laboratory finding in children who have a lumbar puncture for other reasons. Our findings also show that the true risk of a neurological event attributable to the Urabe strain is higher than that estimated from laboratory-ascertained cases of aseptic meningitis[1] (about 1 in 10 000 doses), since affected children often present with only a febrile convulsion and are not investigated by lumbar puncture. The analysis of admissions coded as aseptic meningitis gave an estimated absolute risk of 1 in 15 000 doses for the 15–35-day period. This is similar to the previous estimate of 1 in 21 000 doses based on hospital-ascertained cases in the Oxford region[1] and shows that our method is reliable.

We demonstrated a causal association between ITP and MMR vaccination, with an absolute risk of 1 in 24 000 doses and an attributable risk of 1 in 29 000 doses. ITP is a potentially serious complication which may persist for some months and require treatment with intravenous gammaglobulin, platelet transfusions, or corticosteroids.[7] Until July, 1993, only 20 cases of ITP after MMR vaccine in children aged 1–2 years had been passively reported to the UK Committee on Safety of Medicines, giving an estimated absolute risk of 1 in 130 000 doses and indicating a 5-fold level of under-reporting. 1 of the 4 ITP cases in our study, and 10 of the 11 passively reported ITP cases with batch information happened after Urabe vaccines. This finding indicates that the complication is not mumps-strain specific and is consistent with the view that ITP results largely from the rubella component of the vaccine.[7]

Our study demonstrates the value of using record linkage methods for identifying vaccine-attributable adverse events and for providing reliable estimates of relative incidence and risk. Unlike other attempts to use hospital records to identify neurological complications of vaccines,[8–10] our method allows powerful statistical analysis based only on the children admitted and does not need vaccination dates for the entire population cohort of children. Bias because of a higher probability of admitting children known to have recently been vaccinated could inflate the estimated risks and RIs. However, such bias is unlikely to occur 15–35 days after MMR vaccination, and is not consistent with the dose effect found for DTP vaccination. Bias because of rescheduling of vaccination in unwell children would underestimate the true vaccine effect,[11] but in practice is unavoidable other than in a randomised controlled trial. Randomly missing vaccination records do not bias the RI calculations but cause absolute and attributable risks to be underestimated. The variation between districts in the proportion of admissions linked to vaccination records reflects the extension of hospital catchment areas beyond district boundaries and illustrates the need for record linkage over broader geographical areas. A larger study is now in progress to link all paediatric hospital admission records with immunisation records held on two regional computers. This will allow identification of any admission within defined post-vaccination periods irrespective of ICD code and will provide the necessary control data to test for significant temporal clustering of codes of interest. We hope that our regional study will form the basis of a new national system for the routine monitoring of vaccine safety.

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