SHORT REPORT

Idiopathic thrombocytopenic purpura and MMR vaccine

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Abstract

A causal association between measles–mumps–rubella (MMR) vaccine and idiopathic thrombocytopenic purpura (ITP) was confirmed using immunisation/hospital admission record linkage. The absolute risk within six weeks of immunisation was 1 in 22 300 doses, with two of every three cases occurring in the six week post-immunisation period being caused by MMR. Children with ITP before MMR had no vaccine associated recurrences.

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Cases of idiopathic thrombocytopenic purpura (ITP) occurring within a few weeks of measles–mumps–rubella (MMR) immunisation were first reported and clinically described by Scandinavian workers,[1–3] although an association between thrombocytopenia and measles immunisation had been reported previously.[4] A causal relation between MMR immunisation and thrombocytopenia was accepted in the 1994 Institute of Medicine Report, apparently on the grounds of biological plausibility.[5] The first controlled study[6] found evidence of an increased risk of ITP with onset 15–35 days after immunisation, but was based on only four vaccine associated cases (that is, cases within this risk period). We report an extended study, using record linkage methods in two regions in England, conducted to refine the risk estimates, compare the clinical features of the vaccine and non-vaccine associated cases, and investigate whether children diagnosed with ITP prior to MMR immunisation were at increased risk of a vaccine associated recurrence.

Methods

All hospital admissions for children aged under 5 years in the South East Thames (between October 1991 and September 1994) and North East Thames regions (January 1991 to March 1994), with an ICD 9 discharge code 278.3 were identified from regionally held computerised hospital episode records. This information was linked to immunisation data held on the regional child health computer system. Case notes for children with a linked MMR immunisation record and an admission for ITP in the second year of life were reviewed.

The relative incidence (RI) of an admission for ITP in children aged 12–23 months within the risk period 0–42 days after MMR immunisation compared with the control period was calculated by Poisson regression conditional on the number of admissions for each child,[7] with inclusion of cases from the earlier study in five English districts.[6] The control period was defined as that time before or after MMR immunisation not included in the risk period. Absolute risk of an admission for ITP was calculated by dividing the number of admissions in the risk period by the total number of COVER estimated[8] doses of MMR vaccine given in the hospital catchment areas, adjusting for the proportion of cases which matched with MMR immunisation records.

Results

A total of 45 admissions for ITP were identified in 36 children aged 12 to 23 months in the two study regions, of whom 24 (67% of children and 69% of ITP admissions) had a linked immunisation record. Case notes were traced for all 24 children, three of whom were found not to have had an admission for ITP in the second year of life. One of these children had congenital thrombocytopenia and was admitted with vomiting. A second child had an earlier admission for ITP at 10 months of age but the admission in the second year of life was for an unrelated condition. The third child was admitted for diarrhoea and was found to have a low platelet count of uncertain origin. None of these three cases occurred within 42 days of MMR. After removal of these cases, there were 28 verified admissions for ITP in the second year of life in 21 children with MMR immunisation records. Of these, nine were admitted within 42 days of MMR; none of these nine children had a prior or subsequent admission for ITP in the second year of life. The remaining 19 admissions occurred in 12 children; readmissions occurred at intervals ranging from 15 days to five months. Table 1 shows clinical features of the vaccine associated and non-vaccine associated admissions. The vaccine associated cases tended to be milder with a shorter duration of stay and higher platelet counts. Non-vaccine associated cases showed a predominance of males.

Table 1 Characteristics of vaccine and non-vaccine associated cases of ITP in children aged 12–23 months

	Vaccine associated cases (nine admissions in nine children)	*Non-vaccine associated cases (19 admissions in 12 children)*
Sex ratio (females:males)	5:4	4:8
Median (range) length of admission (days)	3 (1–10)	5 (1–10)
Platelet count during admission		
<20 000	67%	81%
<50 000	78%	94%
Treatment during admission		
Steroids	4/9	8/19
Intravenous immunoglobulin	0/9	3/19
Platelet transfusion	2/9	12/19
Bleeding	5/9	4/19

When combined with the cases from the earlier study, there was a total of 35 children with MMR histories who between them had 44 admissions for ITP during the second year of life. Figure 1 shows the onset of each episode in relation to time of administration of MMR vaccine; in total, 13 of the episodes occurred within the six week period after MMR immunisation (range 11–38 days, median 25).

The relative incidence (RI) of an admission for ITP in the six week post-immunisation risk period compared to the control period was significantly greater than one (RI 3.27, 95% confidence interval (CI) 1.49 to 7.16). The attributable fraction of cases occurring in this period was 0.69—that is, nine of the 13 cases were attributable to MMR, and four to background risk. When divided into three two-week periods, the highest relative incidence in the six weeks after MMR was found between 15 and 28 days (RI 5.80, 95% CI 2.30 to 14.6).

In the earlier study the four vaccine associated cases were detected in a cohort of 1–2 year olds who had received 97 300 doses of MMR[6]; in the new regional study, the nine vaccine associated cases were detected in a cohort who had received a total of 193 000 doses of MMR vaccine (based on birth cohort and vaccine coverage figures[8] and after allowance for the non-match rate of immunisation records with admissions). The absolute (observed) risk of an admission for ITP within six weeks of MMR was 1 in 22 300 doses and the attributable risk (difference between absolute risk and the background rate of ITP in this age group) was 1 in 32 300.

In the combined datasets there were a total of 14 children aged 12–23 months who had a first episode of ITP in the second year of life prior to MMR immunisation; none of these children had a repeat episode within six weeks of immunisation, although three had further episodes unrelated to MMR vaccine. The data from the regional study allowed ascertainment of ITP episodes in all children under 5 years of age. This revealed a further seven children admitted with ITP in the first year of life (excluding neonatal conditions), all of whom subsequently received MMR vaccine. None of these children had a vaccine associated recurrence, although one had a further admission for ITP unrelated to MMR.

Discussion

Our study confirms a causal association between MMR vaccine and ITP. The best estimate of absolute risk within six weeks of MMR is 1 in 22 300 doses, with two of every three cases being vaccine attributable. This is similar to previous estimates,[6] but is considerably less than ITP after natural measles (common), rubella (about 1 in 3000 cases), or mumps (rare). Over 70% of cases of ITP follow virus infections.[9]

The component of MMR vaccine which is responsible for vaccine associated ITP is uncertain, but both the measles[4] and rubella components[3] are likely candidates.

Our results provide clear evidence that children with a history of ITP prior to the first dose of MMR vaccine are not at increased risk of a vaccine associated episode. Moreover the vaccine associated cases tended to be milder than others and not associated with a subsequent recurrence. A history of ITP should not therefore be considered a contraindication to MMR immunisation. Although there have been occasional case reports of children with ITP after repeated doses of MMR or measles containing vaccines,[4 10] there has been no systematic study of the outcome where a second dose of MMR is given to a child who developed

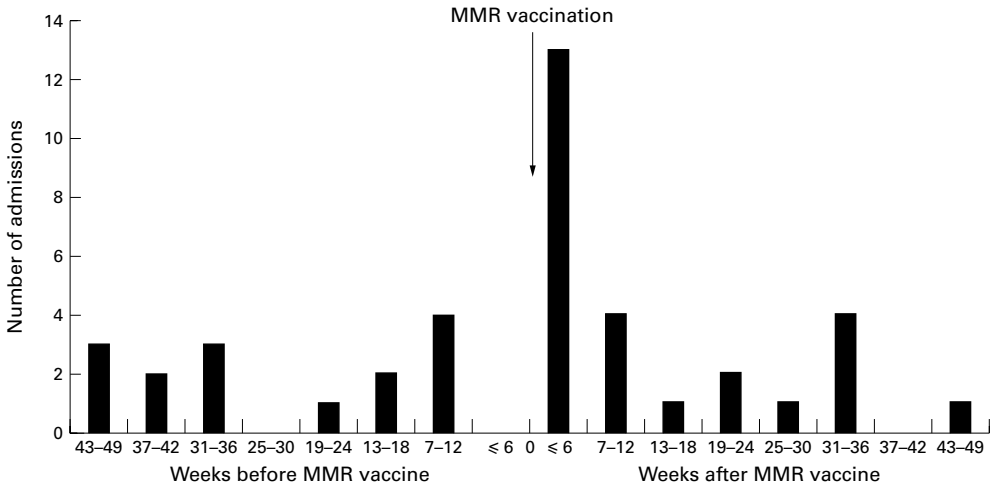

Figure 1 Episodes of ITP in children aged 12–23 months: interval from MMR vaccination (excludes three episodes with intervals greater than 365 days).

ITP after the first dose. We plan to investigate this using record linkage methodology following the introduction of the second dose of MMR in 1996. The recommendation of the American Committee of Immunization Practices does not absolutely contraindicate a second dose of MMR vaccine in children who develop ITP after the first dose, although it suggests that under these circumstances serological evidence of measles immunity may be sought as an alternative to repeat MMR immunisation.[11] The logic of this recommendation is unclear. If, as seems likely, vaccine associated ITP is usually related to susceptibility to the measles or other component of the vaccine with consequent viral replication, then seropositive children should be without risk while reimmunisation of those who are seronegative would be recommended on the grounds of protection against the wild virus infection. Information on the outcome of reimmunisation in children with a history of vaccine associated ITP is required in order to formulate a rational policy.

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Renal vein thrombosis

The prognosis for infants with renal vein thrombosis has improved over the past three or four decades. At one time early thrombectomy or nephrectomy were considered necessary but more recently such procedures have been avoided and anticoagulant treatment or thrombolysis have been used. A report from the Montreal Children's Hospital (Andrew Zigman and colleagues. *Journal of Pediatric Surgery* 2000;**35**:1540–2) describes 23 children diagnosed by Duplex ultrasound scan in the 1990s.

There were 12 boys and 11 girls. One child was 14 years old but the mean age of the others was 13 days and 19 were under 1 month. Only three had the classical triad of palpable abdominal mass, heavy haematuria, and thrombocytopenia. In five cases the renal vein thrombosis was bilateral and in 12 the thrombosis extended into the inferior vena cava. Five infants were considered to have had renal vein thrombosis in utero and three of these were heterozygotes for factor V Leiden. Antenatal risk factors (fetal distress, maternal diabetes, traumatic birth, antenatal steroids, pre-eclampsia, polyhydramnios, amphetamine, protein C deficiency) were identified in 15 cases and postnatal (respiratory distress, heart disease, diarrhoea, hypotension, polycythaemia, factor V Leiden) in 17.

Twelve patients were treated with heparin or enoxaparin and four of these developed long term renal impairment. All 11 not treated with heparin or enoxaparin developed long term renal impairment. Neither thrombolysis nor thrombectomy was attempted and no patient needed dialysis or transplantation. One late nephrectomy was performed for recurrent pyelonephritis.

Heparin treatment is beneficial for infants with renal vein thrombosis. Infants who suffered from renal vein thrombosis in utero should be tested for factor V Leiden.

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