MMR vaccine and idiopathic thrombocytopaenic purpura

Corri Black,[1,2] James A. Kaye,[2] Hershel Jick[2]

[1]*Department of Public Health, Aberdeen University, Aberdeen, UK;* [2]*Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Muzzey Street, Lexington, USA*

Aims To estimate the relationship between idiopathic thrombocytopaenic purpura (ITP) and the measles, mumps and rubella (MMR) vaccination in children; calculating the relative risk estimate for ITP with in 6 weeks after MMR vaccination and the attributable risk of ITP within 6 weeks after MMR vaccination.

Methods Using the General Practice Research Database we identified children with a first-time diagnosis of ITP from a base population of children aged less than 6 years between January 1988 and December 1999. After describing the characteristics of all the children identified with ITP, we focused on cases aged 13–24 months to perform a population-based, case–control analysis to estimate the relative risk of developing ITP within 6 weeks after MMR vaccination. We also calculated the risk of ITP attributable to the MMR vaccination.

Results Sixty-three children with a first time diagnosis of ITP were identified; 23 cases were between 13 and 24 months old. The relative risk estimate for ITP within 6 weeks after MMR vaccination, compared to the combined group of unvaccinated children and children vaccinated with MMR more than 26 weeks previously was 6.3 (95% CI 1.3–30.1). The attributable risk of developing ITP within 6 weeks after MMR vaccination was estimated to be 1 in 25 000 vaccinations (95% confidence interval 21 300, 89 400).

Conclusion This study confirms the increased risk of ITP within 6 weeks after MMR vaccination. However, the attributable risk of ITP within 6 weeks after MMR vaccination is low.

Keywords: idiopathic thrombocytopaenic purpura, MMR vaccine

Introduction

Idiopathic thrombocytopaenic purpura (ITP) is an autoimmune condition resulting in increased platelet destruction. The incidence of ITP among children in the UK is reported to be around 4 per 100 000 per year and is usually self-limiting, although occasional deaths have occurred [1]. ITP has been associated with viral infections and with a variety of vaccinations during childhood [2, 3]. Case reports describe ITP in close time association with the measles, mumps and rubella (MMR) vaccination; in particular, within 6 weeks of vaccination [4–7].

Miller *et al.* [8] recently studied hospital admissions of 1-year-old children with a diagnosis of ITP in seven health board regions in England, and used record linkage to regional child health registries in order to establish the vaccination history of potential cases. The authors identified a peak in the number of cases of ITP within 6 weeks after MMR vaccination (so-called 'vaccine-related' ITP). Thirteen children developed ITP during this time period [relative incidence 3.27; 95% confidence interval (CI)1.5, 7.1]. They estimated the attributable risk of ITP within 6 weeks of MMR vaccination to be 1 in 32 300 vaccinations [8].

The aim of this study was to evaluate the relationship between ITP and MMR vaccination in children registered with the UK General Practice Research Database (GPRD) using a case–control study design, and to provide an estimate of the background risk of nonvaccine-related ITP among children.

Methods

The GPRD has been described in several previous publications [9, 10]. The quality and completeness of the data collection is regularly assessed and validation studies have been published [11, 12]. Practices not meeting the necessary standards of data collection for research have been

Correspondence: Dr Corri Black, Department of Public Health, Aberdeen University, Polwarth Building, Forrester Hill, Aberdeen AB25 2ZD, UK Fax: +44 1224 662994; E-mail: corri.black@abdn.ac.uk

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excluded. The recording of vaccine data, in particular, is virtually complete [13, 14]. Two hundred and eighty-eight general practices contributing to data collection between 1988 and 1999 were included in this study. All data is anonymized with regard to patient and GP identification.

For the current study we identified a base population of all children aged less than 6 years old, enrolled in the GPRD within 4 months of birth, and born between 1 January 1988 and 31 December 1999. As an initial broad search, we identified children with a first-time diagnosis of thrombocytopaenia (International Classification of Disease 287.1) from the base population.

Review of the computer records by two investigators, blinded to the MMR vaccination status, enabled exclusion of children with illnesses predisposing to thrombocytopaenia or purpura (i.e. not idiopathic thrombocytopaenic purpura). These included bone marrow failure, congenital thrombocytopaenia, severe malabsorption, severe sepsis and neonatal thrombocytopaenia. Sixty-five children were considered to have a first-time diagnosis of idiopathic thrombocytopaenic purpura recorded in their computer records. Further anonymized medical records regarding the diagnosis were requested. The date of the first recorded diagnosis of ITP in the computer record was assigned as the index date.

Case–control study

For the case–control study, we focused on some 165 000 children aged 13–24 months. Greater than 90% of children at risk of developing 'possible MMR vaccine-related' ITP (i.e. children within 6 weeks after first MMR vaccination) were within this age group. The median age of first MMR vaccination among children registered with the GPRD is 13 months.

To each case aged 13–24 months we matched up to six controls by age at index date (within 1 month), practice and sex. The index date for each case was assigned as the index date for the matched controls and the same exclusion criteria were applied.

Exposure to MMR vaccine was noted, and the time interval between vaccination and the index date determined from the computer records. We referred to ITP cases that occurred within 6 weeks after an MMR vaccine as 'possible vaccine-related' cases because Miller *et al.* found an association between MMR exposure and ITP during the 6 weeks after MMR vaccination [8], and because this is a plausible period of risk related to a primary immune response [12]. We also evaluated the risk of ITP during a longer period after MMR vaccination (7–26 weeks). For calculation of relative risks, the reference exposure group was a combination of children who had not yet received MMR vaccination before their index date and children who had received MMR vaccination more than 26 weeks before their index date.

We conducted a nested case–control analysis to evaluate whether there was any relationship between recent MMR vaccination and the risk of ITP. Because the data were sparse, we grouped case–control sets by 3-month age bands (13–15 months, 16–18 months, and so on). In addition, we included boys and girls in sets together because childhood ITP is reported to occur with equal frequency among both sexes [13, 14], and because preliminary analysis of our data showed no evidence for a predominance of cases among either sex. The relative risk of ITP during the specified time periods after MMR vaccination was estimated as the odds ratio using conditional logistic regression. (PHREG procedure; SAS version 8; SAS Institute Inc., Cary, NC, USA).

Incidence of ITP among 13- to 24-month-old children

We estimated the absolute and attributable risks of ITP during the 6 weeks after MMR vaccination.

The attributable risk of ITP in relationship to MMR vaccination was estimated by the formula

$$AR = (RR-1)/RR$$

where 'RR' is the relative risk for the relevant time period. Using Poisson regression, we assessed the trend in yearly incidence of ITP among children aged 13–24 months over the 11-year period of the study (Stata, version 7.0; Stata Corporation, College Park, TX, USA) and calculated the 'background' risk of ITP among this age group.

Results

Characteristics of ITP and relationship to MMR in base population

Sixty-five children were identified as potential cases of ITP from the computer records. Medical records were available for 41/65 (63%) children. The diagnosis of thrombocytopaenia recorded in the computer record was confirmed to be ITP in 39/41 (95%) children after medical record review. Two children, in whom ITP was not confirmed, were excluded from further analysis. Medical records were unobtainable for 24 children either because he child had transferred out of the practice or the practice chose not to provide additional medical records for research purposes any longer. These children were considered to be 'probable' cases.

Therefore, 63 children less than 6 years old were considered as having a first-time diagnosis of ITP. Fifty-two of these children (82.5%) had received an MMR vaccination before their index date. Characteristics of the 63

children with ITP in the base population are listed in Table 1. ITP occurred with similar frequency in boys and girls. Fifty children (79%) had mild disease with no complications. None of the 13 children with bleeding were haemodynamically unstable or required blood transfusion, and no child with ITP died. Although most children with ITP were referred to hospital, 11/63 (17.5%) were managed as outpatients, with no hospital admission.

Among the 52 children who developed ITP at some time after having MMR vaccination, only three had recurrences of ITP, and these recurrences were unrelated to any subsequent MMR vaccination. Eleven children developed ITP without having a previous MMR vaccination; seven were subsequently vaccinated with MMR and none developed a recurrence of ITP.

Table 1 Characteristics of children with ITP.

Outcomes	*No. of cases (n = 63)*
Age (at diagnosis)	
0–12 months	6
13–24 months	23
25–36 months	10
37–48 months	9
49–60 months	7
61–72 months	8
Sex	
Male	35
Female	28
Platelet count	
Platelets <20	29
Platelets 20–100	10
Unknown	24
Management	
Hospitalized	33
Outpatient	11
Unknown	19
Treatment	
None	18
Immunoglobulin	13*
Steroids	11
Unknown	23
Complications	
Active bleeding**	13
Serious complications	0
Recurrence	
Yes	3
No	60

*Two children received both steroids and immunoglobulins. **Includes epistaxsis(5), mouth blisters(2), gastrointestinal bleeding(2), other(4).

Case–control study

Twenty-three children aged 13–24 months developed ITP. Eight of the 23 children in this age range developed ITP within 6 weeks after receiving their first MMR vaccination ('possible vaccine-related' ITP). Seven of these events occurred between day 7 and day 28 after vaccination.

The 23 cases were matched, by age (within 1 month), sex, practice and index date, to 116 controls. For calculation of relative risks, we used a combined reference exposure group of children who had not received MMR vaccination before their index date and children who had received MMR vaccination more than 26 weeks before their index date (Table 2). The estimated relative risk of 13–24-month-old children developing ITP during the period within 6 weeks after MMR vaccination, compared to the reference group, was 6.3 (95% CI 1.3, 30.1). In contrast, the estimated relative risk during the period from 7 to 26 weeks after MMR vaccination was not significantly elevated. Estimating the relative risk (RR), excluding 'probable cases' where medical records were not available to confirm the diagnosis of ITP, did not materially change the relative risk estimate.

Review of computer records and additional documents of the eight children with vaccine-related ITP showed no evidence of infection, other illness, or other drug exposure during the month before MMR vaccination, nor during the weeks between vaccination and the diagnosis of ITP. Although two of the eight children with vaccine-related ITP subsequently received a second MMR vaccination, neither experienced a recurrence of ITP.

Table 2 Vaccination exposure and estimated relative risk of ITP after MMR vaccination among 13–24-month-old children.

Vaccination exposure	*Cases (n = 23)*	*Controls (n = 116)*	*Relative risk*	*95% CI*
Reference group [unexposed to MMR or > 26 weeks after MMR]	9 (39.1%)	65 (56.0%)	Reference	–
6 weeks or less after MMR vaccination	8 (34.8%)	19 (16.4%)	6.3	1.3, 30.1
7 to 26 weeks after MMR	6 (26.1%)	32 (27.6%)	1.5	0.4, 4.8

Table 3 Yearly incidence of ITP among 13–24-month-old children.

Year	Cases	Person-time	Yearly incidence rate (per 10 000) and confidence interval
1989	0	6 378	0 (0, 5.8)
1990	0	14 530	0 (0, 2.5)
1991	2	16 772	1.2 (0.1, 4.3)
1992	5	20 829	2.4 (0.8, 5.6)
1993	5	19 745	2.5 (0.8, 5.9)
1994	0	20 521	0 (0, 1.8)
1995	4	19 252	2.1 (0.6, 5.3)
1996	4	15 612	2.6 (0.7, 6.6)
1997	2	10 822	1.8 (0.2, 6.7)
1998	1	8 307	1.2 (0, 6.7)
1999	0	1 918	0 (0, 19)

*95% two-sided confidence interval or 97.5% one-sided confidence interval (for years in which there were no cases).

Incidence of ITP among 13- to 24-month-old children

The estimated absolute risk of developing ITP during the 6 weeks after MMR vaccination was 1 in 21 000 (95% CI 10 500, 47 800) vaccine doses. The estimated attributable risk of developing ITP during the 6 weeks after MMR vaccination was 1 in 25 000 (95% CI 21 300, 89 400) vaccine doses.

No trend was detected in the yearly incidence rate of ITP among 13–24-month-olds over the 11 years of the study (Table 3).

Fifteen of the 23 cases of ITP among 13–24 month-olds occurred in children who had not received MMR vaccination or who received MMR vaccination more than 6 weeks before their index date. The estimated 'background' rate of ITP (unrelated to MMR vaccination) among children aged 13–24 months was 0.9 per 10 000 person-years (95% CI 0.5, 1.5).

Discussion

We estimated the background rate of ITP among 13–24-month-old children to be 0.9 in 10 000 person-years. We found an approximately six-fold increase in risk of ITP in 13–24-month-old children during the 6 weeks following MMR vaccination. Seven of the eight vaccine-related cases of ITP occurred between week 2 and week 4 after vaccination. The risk of developing ITP during the 6 weeks after MMR vaccination attributable to the vaccine was estimated to be 1 in 25 000 vaccine doses. (The attributable risk is calculated for a 6-week time period and should not be compared directly to the background incidence rate for ITP, which is the estimated average risk over the 1-year age period under study in the absence of recent MMR vaccination.) The estimated RR during the period from 7 to 26 weeks after MMR vaccination was not significantly elevated [RR 1.5 (95% CI 0.4, 4.8)] but with broad confidence intervals, the data are compatible with a longer risk period.

Like the study by Miller *et al.* [8], our study provides additional evidence of the association between ITP and MMR vaccination. We found a higher relative and attributable point estimate risk of ITP within 6 weeks of MMR vaccination than Miller *et al.,* although the confidence intervals are wide and overlapping. While there is no statistically significant difference, two aspects in the study design may have contributed to a difference in relative and attributable risk. Miller *et al.* relied only on hospital admission data, but by using the GPRD, we were able to identify children managed as outpatients. Miller *et al.* also found only 67% of the children admitted to hospital with ITP could be linked to a vaccination history in the child health registry. The GPRD has been found to have virtually complete recording of vaccine histories and a consistently high proportion of children registered to practices contributing to the GPRD have been found to be vaccinated with MMR [14]. By restricting our study to children registered with a GP within 4 months of birth we are confident that we have complete vaccine histories for all of the cases and controls in this study.

In an attempt to reduce bias, the identification of cases and controls was carried out by two reviewers blinded to the vaccine exposure of the subjects, who independently assessed the computer records and available case records for children with potential ITP. The diagnosis code for ITP in the computer records were confirmed by hospital discharge letter in 95% of available case records, again confirming the high quality of data recording by GPs contributing the GPRD.

During the study period of 1988–99 the vaccination rate among children registered with the GPRD has been constant around 94% [14]. Similarly, no statistically significant trend in the rate of ITP among 13–24-month-old children was found during this time period. This contrasts to the time trend analysis, published by our group, regarding autism and MMR vaccination over a similar time period. The incidence of autism was shown to increase steeply over time while MMR vaccination rates were virtually constant [14].

This study confirms that ITP below the age of 6 years old is generally a mild disease, with few serious bleeding episodes or long-term sequele, despite the low platelet counts found in many of the children. Most children presented with bruising and petechiae. Five had minor epistaxis and two had minor gastrointestinal bleeds but none were haemodynamically compromised or required blood transfusion. Recurrence of ITP among the children studied was uncommon. Of the 11 children who

developed ITP prior to MMR vaccination, none developed a recurrence after subsequent vaccination.

Of the eight children with MMR vaccine associated ITP, two went on to receive a second MMR vaccination without recurrence.

Conclusion

Although ITP is one of the most frequently diagnosed haematological disorders among young children, it is an uncommon condition. The risk of ITP occurring within the 6 weeks after vaccination with MMR is significantly increased. However the attributable risk of ITP within 6 weeks after MMR vaccination remains low at 1 in 25 000 vaccinated children. Complications or long-term consequences of ITP in this age group are rare. For the majority of children less than 6 years of age, the illness is self-limiting.

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