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Pediatrics 2008;121:e687-e692

DOI: 10.1542/peds.2007-1578

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/121/3/e687>

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American Academy of Pediatrics

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Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

BACKGROUND. The measles-mumps-rubella vaccine has been associated with immune thrombocytopenia purpura in 2 small studies.

METHODS. By using the Vaccine Safety Datalink, we identified measles-mumps-rubella-vaccinated children aged 1 to 18. A case of immune thrombocytopenia purpura was defined as a patient with a platelet count of $\leq 50\ 000/\mu\text{L}$ with clinical bleeding and normal red and white blood cell indices. The immune thrombocytopenia purpura incidence rates during exposed (42 days after vaccination) and unexposed time periods were determined. A retrospective cohort of vaccinated children was used to determine incident rate ratios for children aged 1 to 18 years, 12 to 23 months, and 12 to 15 months.

RESULTS. A total of 1 036 689 children received 1 107 814 measles-mumps-rubella vaccinations; there were 259 confirmed patients with immune thrombocytopenia purpura. Because only 5 exposed cases occurred after age 2, analyses were limited to children aged 12 to 23 months. Exposed patients aged 12 to 23 months had lower median platelet counts than those who were unexposed and had similar median duration of illness (11 vs 10 days). The incident rate ratio was highest for children aged 12 to 15 months at 7.10. The incident rate ratio for boys aged 12 to 15 months was 14.59, and the incident rate ratio for girls in the same age group was 3.22. Seventy-six percent of immune thrombocytopenia purpura cases in children aged 12 to 23 months were attributable to measles-mumps-rubella vaccination. This vaccine causes 1 case of immune thrombocytopenia purpura per every 40 000 doses.

CONCLUSION. Measles-mumps-rubella vaccine that is given in the second year of life is associated with an increased risk of immune thrombocytopenia purpura.

IN 1993, THE Vaccine Safety Committee of the Institute of Medicine concluded that a causal relationship exists between the measles-mumps-rubella (MMR) vaccine and thrombocytopenia.¹ This conclusion was made on the basis of a known relationship between wild-type measles infection and thrombocytopenia, numerous case reports that have described thrombocytopenia after MMR vaccination, and epidemiologic data from Sweden and Finland that have demonstrated higher-than-expected incidence rates of thrombocytopenia during the weeks after MMR immunization. No controlled studies comparing incidence rates of thrombocytopenia after MMR exposure to unexposed time periods were available.

www.pediatrics.org/cgi/doi/10.1542/peds.2007-1578

doi:10.1542/peds.2007-1578

This study was presented in part at the European Society for Paediatric Infectious Disease meeting; May 19, 2005; Valencia, Spain.

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Key Words

immune thrombocytopenia purpura, children, measles-mumps-rubella vaccines, thrombocytopenia

Abbreviations

MMR—measles-mumps-rubella
ITP—immune thrombocytopenic purpura
IRR—incident rate ratio
CI—confidence interval
VSD—Vaccine Safety Datalink
CDC—Centers for Disease Control and Prevention
MCO—managed care organization
ICD-9—*International Classification of Diseases, Ninth Revision*
SCCS—self-controlled case series

Accepted for publication Nov 30, 2007

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2008 by the American Academy of Pediatrics

Since 1993, several additional published case reports have alluded to this causal link,²⁻⁴ and 2 small controlled investigations from England have presented quantitative evidence that supports this relationship.^{5,6} Miller et al⁵ identified 35 children aged 12 to 23 months who were hospitalized for immune thrombocytopenic purpura (ITP) and found an increased incidence of ITP in the 6 weeks after MMR immunization (incident rate ratio [IRR]: 3.27; 95% confidence interval [CI]: 1.49–7.16). A second study by Black et al⁶ identified 23 children aged 12 to 24 months with a diagnosis of ITP and demonstrated an increased risk of ITP in the 6 weeks after MMR vaccination (odds ratio: 6.3; 95% CI: 1.3–30.1).

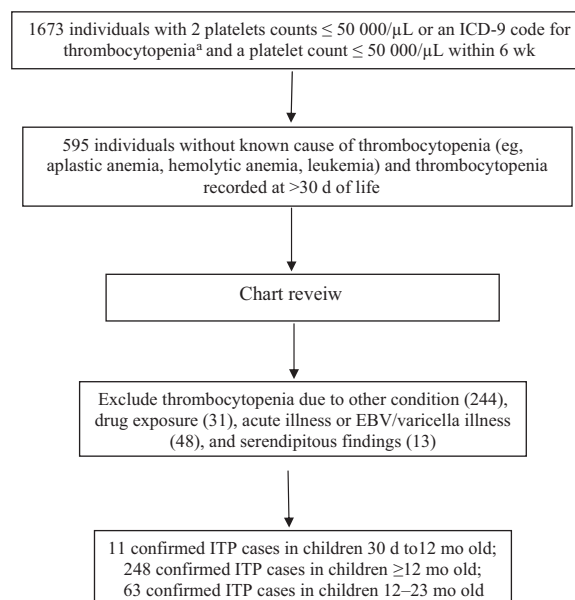
Although these 2 studies provided controlled data that showed an association between MMR immunization and ITP, they had a number of limitations. First, both studies were small, and their focus was limited to children in the second year of life. Second, neither study described the exclusion of thrombocytopenia cases attributable to exposures known to cause this condition (eg, drugs such as sulfa antibiotics or viral infections such as varicella) or where results were found serendipitously (eg, a low platelet count discovered in an asymptomatic child on a routine complete blood count). Third, neither study clearly differentiated between new-incident cases and ongoing illness. Finally, neither study provided information on the risk of developing chronic ITP. The aim of our study was to evaluate the risk of ITP after MMR immunization in a large population of children aged 12 months to 18 years.

METHODS

Data from the years 1991–2000 were extracted from the Vaccine Safety Datalink (VSD), a project established in 1991 by the Centers for Disease Control and Prevention (CDC) to evaluate the safety of vaccines.⁷ The VSD links large databases that contain information on vaccination history, medical encounters (inpatient and outpatient), and demographics from 8 managed care organizations (MCOs) located across the United States. During the study period, there were >2 million children enrolled in the VSD cohort. Seven MCOs provided data for children up to 18 years of age, whereas the eighth MCO provided data only for children aged 12 to 23 months. The institutional review board of each study site and the CDC approved this study.

Case Ascertainment

The criteria for cases were defined as children aged <18 years with a platelet count of $\leq 50\,000/\mu\text{L}$ with normal red and white blood cell indices, the presence of clinical signs and symptoms of spontaneous bleeding, and the absence of fever. A case was excluded if in the 6 weeks before diagnosis the child was exposed to platelet-depleting medication (phenytoin, valproic acid, or sulfonamide antibiotics) or infected with wild-type varicella or Epstein-Barr virus. Asymptomatic cases (ie, no signs or symptoms of bleeding) found serendipitously, such as a low platelet count found on a complete blood count screening for anemia, or as part of a preoperative eval-



ICD-9 Code	Category
287.0	Allergic purpura
287.1	Qualitative platelet defects
287.2	Other nonthrombocytopenic purpura
287.3	Primary thrombocytopenia ^b
287.4	Secondary thrombocytopenia ^c
287.5	Thrombocytopenia, unspecified
287.8	Other specified hemorrhagic conditions
287.9	Unspecified hemorrhagic conditions

FIGURE 1

Case ascertainment. EBV indicates Epstein-Barr virus. ^a ICD-9 codes for ascertainment screening; ^b includes congenital, hereditary, and idiopathic thrombocytopenic purpura and thrombocytopenia; ^c includes thrombocytopenia caused by dilutional, drugs, extracorporeal circulation of the blood, and platelet alloimmunization causes.

uation were excluded, as were children who were ill at presentation (ie, fever, vomiting/diarrhea, seizure). Because US policy does not routinely recommend MMR vaccination before 1 year of age, the likelihood of being exposed to MMR before the age of 1 is low; therefore, children diagnosed before the age of 1 were excluded from the primary analysis but included when assessing the risk of recurrence after MMR vaccination among children with a history of previous ITP.

The ITP resolution date was determined by reviewing medical charts and defined as the date of the first platelet count of $>100\,000/\mu\text{L}$ with no evidence of a drop in platelet count in subsequent weeks. A case of ITP was considered chronic if the thrombocytopenia lasted >6 months or if notes in the medical chart dated >6 months after diagnosis described the ITP as chronic.

Cases were ascertained by using 3 steps (Fig 1). Steps 1 and 2 were conducted by using automated databases, with the analyst being blinded to vaccination status. In step 1, an analyst used the VSD to identify children <18 years of age with either 2 platelet counts of $\leq 50\,000/\mu\text{L}$ in a 6-week period or 1 platelet count of $\leq 50\,000/\mu\text{L}$ and an associated *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis code of 287.0 to 287.9 within 6 weeks (Fig 1). In

step 2, we reviewed electronic data to exclude cases of thrombocytopenia from a known condition (eg, neonatal thrombocytopenia, aplastic anemia, defibrination syndrome, acquired hemolytic anemia, chronic liver disease, or malignant neoplasm). In step 3, staff at VSD sites audited patient charts and sent to the principal investigator the completed audit form, photocopies of the patient's medical chart from 6 weeks before through 6 months after ITP diagnosis, and a separate audit form with the MMR vaccination date. A pediatrician (Dr France) blinded to vaccine status repeated the chart audit to confirm the onset date and initial platelet count and to assign the case status and resolution date.

Study Methods

We used 2 analytic methods common to vaccine-safety studies to examine the risk of ITP after MMR vaccination: the risk-interval and self-controlled case series (SCCS). The risk-interval method is considered a modified cohort design in which only vaccinated individuals are included in the analysis, and time periods both before and after vaccination (for the same individual) determine exposure status.⁸ For this design, cases and non-cases with a valid vaccination record are eligible for the analysis. The SCCS method is a case-only design in which each case acts as its own control.^{9,10} Incidence rates of ITP during the exposed and unexposed periods are compared, and conditional Poisson regression models are used to analyze the data. Because cases are compared with themselves, confounding variables such as MCO, ethnicity, and chronic preexisting health disorders are controlled for by proxy. Both the risk-interval and SCCS methods have been shown to be valid and comparable to the traditional cohort and case-control designs.¹¹

We included only children in the VSD cohort who had been vaccinated with MMR while actively enrolled in their respective MCOs. For each child, follow-up time was limited to the 365 days before and after MMR vaccination. Vaccinated children with ITP that occurred outside this follow-up window were excluded. We compared the incidence of ITP during the exposed period, defined as 42 days after MMR vaccination, to the ITP incidence during the unexposed period, defined as the time periods before and after the exposed period. We also excluded the 6 weeks immediately preceding MMR vaccination from analysis, because this time may represent a period when a child is most likely to be healthy (the healthy-vaccinee) and may underestimate the background incidence of ITP.¹² Because a child with ITP cannot become a new case until the current illness resolves, patients diagnosed with ITP did not again contribute person-time to the study until the day after the ITP resolution date.

Analysis

IRRs were planned for children aged 12 months to 18 years, 12 to 23 months, and 12 to 15 months by using both the risk-interval and SCCS methods. Data for the risk-interval method were analyzed with Poisson regres-

sion models, controlling for age, MMR dose number, MCO site, and gender. Age was modeled as a categorical covariate in 3 different 4-month groups: 12 to 15, 16 to 19, and 20 to 23. Deviance and Pearson χ^2 statistics were used to evaluate the models' fit. The attributable risk of ITP due to MMR exposure was calculated as the difference between the incidence rates of exposed and unexposed children aged 12 to 23 months.

The SCCS data were analyzed by using conditional Poisson regression models, controlling for age. Fixed covariates that do not change over time, such as gender, MCO, and MMR dose number, were controlled for by proxy and were excluded from the models. The unvaccinated children were included in the analysis to help provide stable background incidence rates for age.

RESULTS

A total of 1 036 689 children received 1 107 814 MMR vaccinations during the study period; there were >45 million exposed and 430 million unexposed person-days in the study cohort. Fifty-four percent of all doses were given between 12 and 23 months of age. By using electronic databases, we identified 1673 individuals as potential cases (Fig 1). Of these, we excluded 532 who had a known cause of thrombocytopenia (eg, aplastic anemia, leukemia) and 546 who were <30 days of age at the time of diagnosis, which left 595 potential ITP cases for chart review.

Chart review identified 244 patients who did not have ITP and 92 patients who were excluded because of drug exposure ($n = 31$), acute illness ($n = 48$), or serendipitous finding during routine care ($n = 13$); 259 patients met the case definition of ITP, of which 248 were >12 months of age. In 79% of cases, a hematologist was involved to manage the child's care. Of confirmed cases, 82 fell in the predefined follow-up period of 365 days before or after MMR vaccination.

Table 1 describes the clinical characteristics of ITP that are grouped in 4 age ranges. In particular, these data show that a majority (80%) of the MMR-exposed cases occurred in children aged 12 to 23 months. In the older 3 age groups, there were only 5 exposed children: 3 between the ages of 2 and 4 years, 1 between the ages of >4 and 10 years, and 1 >10 years of age. We did not have the statistical power to detect an effect in these ages; thus, we focused the analysis on children aged 12 to 23 months.

Table 2 compares the MMR-exposed ($n = 20$) and unexposed ($n = 43$) patients with ITP aged 12 to 23 months. There were no statistically significant differences in gender, median number of presenting platelet counts, percent with a viral illness or medication exposure in the 6 weeks preceding illness, or median duration of illness. There were no deaths in any group because of complications from ITP. Two of the 20 exposed ITP children aged 12 to 23 months (10%) went on to be classified as having chronic ITP. Among unexposed ITP children aged 12 to 23 months, 3 (7%) of 43 developed chronic ITP. Figure 2 shows the distribution of ITP cases over the second year of life.

For children 12 to 23 months of age, the IRRs for ITP

TABLE 1 Clinical Characteristics of Patients With ITP in the 12- to 23-Month-Old, 24- to 59-Month-Old, 5- to 10-Year-Old, and ≥ 11 -Year-Old Age Groups

Characteristics	Age Group			
	12–23 mo	24–59 mo	5–10 y	≥ 11 y
Total ITP cases, <i>N</i>	63	69	56	60
Gender, <i>n</i> (%)				
Male	33 (52)	31 (45)	30 (54)	29 (48)
Female	30 (48)	38 (55)	26 (46)	31 (52)
Platelet count at diagnosis (25th, 75th percentiles), per μL	7000 (3000, 18 000)	8500 (3000, 18 500)	8000 (3000, 17 000)	7000 (4000, 16 000)
Referral to hematologist, <i>n</i> (%)	52 (83)	51 (74)	48 (86)	48 (80)
Acute illness within 6 wk before diagnosis, <i>n</i> (%)	52 (83)	49 (71)	38 (68)	33 (55)
Medications (any) within 6 wk before diagnosis, <i>n</i> (%)	24 (38)	25 (36)	16 (29)	22 (37)
Diagnosis type, <i>n</i> (%)				
Acute	57 (90)	56 (81)	43 (77)	31 (52)
Chronic	5 (8)	12 (17)	13 (23)	29 (48)
Unknown	1 (2)	1 (2)	0	0
Duration of ITP (25th, 75th percentiles), d	11 (6, 28)	12 (5, 38)	8 (5, 27)	13 (6, 39)
MMR exposed, <i>n</i> (%)	20 (32)	3 (4)	1 (2)	1 (2)

were 3.94 (95% CI: 2.01–7.69) and 5.38 (95% CI: 2.72–10.62) by using the risk-interval and SCCS methods, respectively (Table 3). For children 12 to 15 months of age, the IRRs increased to 7.10 (95% CI: 2.03–25.03) by using the risk-interval method and 7.06 (95% CI: 1.95–25.88) by using the SCCS method. Gender was a strong effect modifier: the IRR for boys aged 12 to 15 months was 14.59 (95% CI: 1.84–114.43) by using the risk-interval method and 12.39 (95% CI: 1.54–99.52) by using the SCCS method, compared with IRRs of 3.22 (95% CI: 0.59–17.64) and 4.07 (95% CI: 0.70–23.77) for girls by using the risk-interval and SCCS methods, respectively. These results are based on 12 boys (9 exposed, 3 unexposed) and 7 girls (4 exposed, 3 unexposed) aged 12 to 15 months.

Of the 599 833 MMR vaccinations administered to children 12 to 23 months of age, 80% were given between the ages of 12 and 15 months, 17% were administered between the ages of 16 and 19 months, and 3% between the ages of 20 and 23 months. Exposed cases

were also distributed unevenly over the second year of life. Of the 20 exposed patients, 13, 6, and 1 were diagnosed in the 12- to 15-, 16- to 19-, and 20- to 23-month age groups, respectively. In the risk-interval analysis, the IRR dropped from 7.10 to 3.94 when the age interval was extended from 12 to 15 to 12 to 23 months. The proportion of ITP cases attributable to MMR exposure among children 12 to 15 months of age was 86%; the attributable risk for children 12 to 23 months of age was 76%. One case of ITP occurred per every 40 000 vaccinations in the 12- to 23- and 12- to 15-month age groups (Table 3).

Including ITP cases that occurred after the first month of life, 31 children were vaccinated with MMR after they developed ITP. None of these children had a recurrence of ITP during the 42 days after MMR vaccination. Two children received MMR vaccination within 8 weeks of their ITP resolution date without consequence. Of the cases occurring between 12 and 15 months of age (a time when MMR exposure is common), evidence that the physician asked about recent vaccination with MMR was present in 2 of 13 cases.

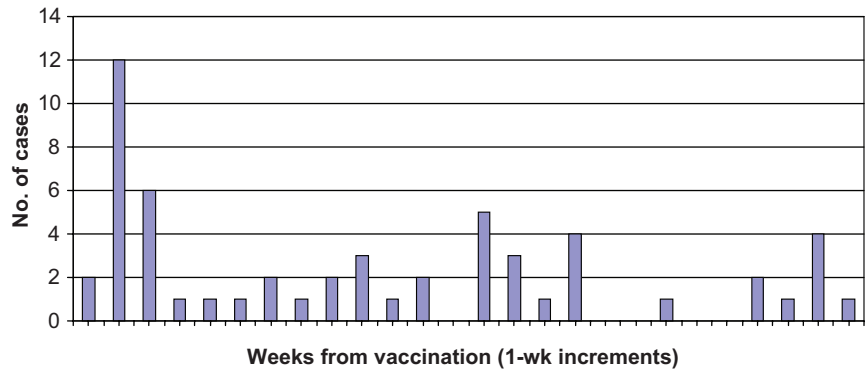
TABLE 2 Characteristics of Patients With ITP Aged 12 to 23 Months According to MMR Exposure Within 42 Days of Diagnosis

Characteristics	Exposed to MMR (<i>n</i> = 20)	Not Exposed (<i>n</i> = 43)
Age (25th, 75th percentiles), y	1.29 (1.12, 1.38)	1.62 (1.38, 1.81)
Female, <i>n</i> (%)	8 (40)	22 (51)
Platelet count at diagnosis (25th, 75th percentiles), per μL	6000 (2500, 10 500)	9000 (4000, 19 000)
Referral to hematologist, <i>n</i> (%)	17 (85)	35 (81)
Acute illness within 6 wk before diagnosis, <i>n</i> (%)	17 (85)	35 (81)
Medications (any) within 6 wk before diagnosis, <i>n</i> (%)	9 (45)	15 (35)
Diagnosis type, <i>n</i> (%)		
Acute	18 (90)	39 (91)
Chronic	2 (10)	3 (7)
Unknown	0	1 (2)
Duration of acute ITP (25th, 75th percentiles), d	11 (6, 28)	10 (6, 28)

DISCUSSION

Our study found a strong association between MMR vaccination and the risk of ITP in children 12 to 23 months of age. This association was strongest among children 12 to 15 months of age and was higher for boys compared with girls. The duration and severity of ITP among exposed children 12 to 23 months of age were not different from those of the unexposed children, and the development of chronic ITP after MMR vaccination seemed rare. Three of every 4 cases of ITP that occurred in the second year of life were attributable to MMR vaccination. Although we had hoped to explore the association of MMR with ITP among children through 18 years of age, we found only a small number of exposed cases after the age of 2 (5 of 507 981 MMR doses given) and were unable to do so. ITP after MMR vaccination

FIGURE 2
Distribution of ITP cases according to weeks from MMR vaccination to ITP onset (12–23 months of age).



seems to be no more severe than cases that occur during unexposed time periods.

Our study revealed elevated risks for ITP among MMR-vaccinated children 12 to 23 months old that were similar in magnitude to the results of Miller et al⁵ (IRR: 3.27) and Black et al⁶ (odds ratio: 6.10). When we focused on children aged 12 to 15 months, the period of recommended MMR vaccination in the United States, we found a stronger association (IRR: 7.1). Because of the skewed distribution of MMR vaccination over the 12- to 23-month age period, in which 80% of immunizations are given in the first 4 months, we believe that the IRRs from the 12- to 15-month analyses are better estimates of the association between ITP and MMR than those generated from the 12- to 23-month analyses.

None of the 31 children with ITP and a subsequent MMR vaccination developed postvaccination ITP, which is consistent with the results of Miller et al⁵, in which 7 children with ITP before they were vaccinated with MMR had no recurrence. Our numbers are too small, however, to warrant firm conclusions as to whether children with a history of ITP have a risk of recurrence with MMR vaccination.

The Brighton Collaboration established a platelet count cutoff of $<150\,000/\mu\text{L}$ as its criteria for thrombocytopenia associated with vaccination, which can be confirmed with a review of the blood smear or when the patient presents with clinical signs and symptoms.¹³ Our definition of ITP was different only in requiring a lower platelet count ($\leq 50\,000/\mu\text{L}$), thus focusing on those children with ITP who were likely to be symptomatic. We chose to define thrombocytopenia by using a platelet level that is more often associated with signs and symp-

oms of bleeding to limit the number of required chart audits and to focus on the more serious ITP outcomes. Although the use of a higher platelet count cutoff would have helped us understand the overall impact of MMR on thrombocytopenia, platelet counts of $>50\,000$ rarely cause signs or symptoms of ITP and are unlikely to be clinically important.

Although the clinical literature suggests that ITP in infants and toddlers occurs more frequently in boys than girls,^{14–17} we were surprised to find the strong gender effect in our data, which is an association not seen in previous studies. This finding should be viewed with caution, given the small number of cases on which it is based (12 boys, 7 girls). It has been shown that male toddlers are at higher risk for injury compared with female toddlers.¹⁸ One-year-old boys may be more active than girls, potentially increasing their chances of bruising if they have thrombocytopenia and leading to a visit to the doctor for evaluation. More visits to the doctor could selectively increase the probability of a male infant with thrombocytopenia being diagnosed with ITP. Female infants with thrombocytopenia, in turn, would have a decreased probability of being diagnosed with ITP, which would reduce statistical power and bias the results to the null hypothesis (ie, toward seeing no increased risk after vaccination). Whether differences in physical activity levels explain our gender findings or if this is a true biological difference is unknown.

It is of no surprise that, after a review of chart data, clinicians often asked about recent viral infections or medication exposure, which are known causes of ITP in children. It was documented that clinicians most asked about a recent viral infection in each of the 13 MMR-

TABLE 3 Association Between the Administration of MMR Vaccination and the Acute Onset of ITP Within 42 Days of Vaccination

Age Group (No. of Exposed, Unexposed)	IRR (95% CI)		
	SCCS	Risk Interval	Attributable Risk
12–23 mo (20, 43) ^a	5.38 (2.72–10.62)	3.94 (2.01–7.69)	39 500 (30 500–48 500)
12–15 mo (13, 6)	7.06 (1.95–25.88)	7.10 (2.03–25.03)	40 300 (32 000–48 600)
Boys (9, 3)	12.39 (1.54–99.52)	14.59 (1.84–114.43)	—
Girls (4, 3)	4.07 (0.7023.77)	3.22 (0.59–17.64)	—

— indicates that data are not available.

^a Adjusted for age in three 4-month age groupings (12–15, 16–19, and 20–23 months).

exposed ITP cases that occurred between the ages of 12 and 15 months and medication exposure in 8 of the 13 cases. In contrast, only 2 of the 13 cases had documented questions that asked about recent MMR vaccination. It seems that clinicians do not think first of exposure to this vaccine when evaluating a 12- to 15-month-old for thrombocytopenia.

CONCLUSIONS

Since its introduction in the 1960s, the MMR vaccine has reduced the incidence of wild-type measles by nearly 100% in the United States.¹⁹ Although this vaccine is associated with an increased incidence of ITP, the attributable risk is low (~1 case per 40 000 doses of MMR), and the disease associated with MMR vaccination is mild and resolves, on average, within 7 days. Our results, therefore, do not suggest a need to alter current immunization policies.

ACKNOWLEDGMENTS

This work was supported by the CDC through an agreement with America's Health Insurance Plans.

We thank the data-management staff at the participating MCOs for their work in putting together the VSD files and the personnel at America's Health Insurance Plans for their assistance.

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Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children

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Pediatrics 2008;121:e687-e692

DOI: 10.1542/peds.2007-1578

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