The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents

AUTHORS: Sean T. O'Leary, MD, MPH,[a,b,c] Jason M. Glanz, PhD,[c] David L. McClure, PhD,[c] Aysha Akhtar, MD, MPH,[d] Matthew F. Daley, MD,[a,c] Cynthia Nakasato, MD,[e] Roger Baxter, MD,[f] Robert L. Davis, MD, MPH,[g] Hector S. Izurieta, MD, MPH,[d] Tracy A. Lieu, MD, MPH,[h,i] and Robert Ball, MD, MPH, Scm[d]

[a]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, Colorado; [b]Children's Outcomes Research Program, Children's Hospital Colorado, Aurora, Colorado; [c]Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado; [d]Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland; [e]Center for Health Research Hawaii, Kaiser Permanente Hawaii, Honolulu, Hawaii; [f]Kaiser Permanente Vaccine Study Center, Oakland, California; [g]Center for Health Research Southeast, Kaiser Permanente of Georgia, Atlanta, Georgia; [h]Center for Child Health Care Studies, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care Institute, Boston, Massachusetts; and [i]Division of General Pediatrics, Children's Hospital Boston, Massachusetts

KEY WORDS
immune thrombocytopenia purpura, children, vaccines, adverse reactions, thrombocytopenia

ABBREVIATIONS
CI—confidence interval
DTaP—diphtheria-tetanus-acellular pertussis vaccine
HBV—hepatitis B virus vaccine
Hep A—hepatitis A vaccine
Hib—*Haemophilus influenzae* type b vaccine
HPV—human papilloma virus vaccine
IPV—inactivated poliovirus vaccine
IRR—incident rate ratio
ITP—immune thrombocytopenic purpura
MCV—meningococcal conjugate vaccine
MMR—measles-mumps-rubella vaccine
MMRV—measles-mumps-rubella-varicella vaccine
PCV—pneumococcal conjugate vaccine
RV—rotavirus vaccine
Tdap—tetanus-diphtheria-acellular pertussis vaccine
TIV—trivalent influenza vaccine
VAR—varicella vaccine

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1111

doi:10.1542/peds.2011-1111

Accepted for publication Oct 6, 2011

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: Studies on vaccine safety are crucial to the ongoing success of our national immunization program. ITP has a known association with MMR in young children, occurring in 1 in 40 000 doses. The risk after other childhood vaccines is unknown.

WHAT THIS STUDY ADDS: This study found no increased risk of ITP after vaccines other than MMR in young children, confirmed an association of ITP with MMR, and also found that ITP may occur after certain other vaccines in older children.

abstract

FREE

BACKGROUND: The risk of immune thrombocytopenic purpura (ITP) after childhood vaccines other than measles-mumps-rubella vaccine (MMR) is unknown.

METHODS: Using data from 5 managed care organizations for 2000 to 2009, we identified a cohort of 1.8 million children ages 6 weeks to 17 years. Potential ITP cases were identified by using diagnostic codes and platelet counts. All cases were verified by chart review. Incidence rate ratios were calculated comparing the risk of ITP in risk (1 to 42 days after vaccination) and control periods.

RESULTS: There were 197 chart-confirmed ITP cases out of 1.8 million children in the cohort. There was no elevated risk of ITP after any vaccine in early childhood other than MMR in the 12- to 19-month age group. There was a significantly elevated risk of ITP after hepatitis A vaccine at 7 to 17 years of age, and for varicella vaccine and tetanus-diphtheria-acellular pertussis vaccine at 11 to 17 years of age. For hepatitis A, varicella, and tetanus-diphtheria-acellular pertussis vaccines, elevated risks were based on one to two vaccine-exposed cases. Most cases were acute and mild with no long-term sequelae.

CONCLUSIONS: ITP is unlikely after early childhood vaccines other than MMR. Because of the small number of exposed cases and potential confounding, the possible association of ITP with hepatitis A, varicella, and tetanus-diphtheria-acellular pertussis vaccines in older children requires further investigation. *Pediatrics* 2012;129:1–8

Immune thrombocytopenic purpura (ITP) was first described after a wild-type measles virus infection in 1952.[1] In 1966, Oski and Naiman reported thrombocytopenia after a live attenuated measles vaccine.[2] Since then, the association of live attenuated measles-mumps-rubella (MMR) vaccine and ITP has been well established.[3–11] ITP is known to occur after many types of infections, including numerous vaccine-preventable diseases.[12–18] In approximately two-thirds of ITP cases, there is a history of a preceding infectious illness in the days to weeks before ITP onset.[19] A subset of these children will have an identifiable virus, such as Epstein-Barr virus, varicella zoster virus, influenza virus, or HIV.[16] Because vaccines are designed to induce an immune response that mimics natural infection to produce immunologic protection, it is theoretically possible that vaccines besides MMR could trigger ITP. In addition, there have been case reports of ITP after other childhood vaccines, including hepatitis B vaccine (HBV), diphtheria-tetanus-pertussis vaccine (DTP), and hepatitis A vaccine (Hep A).[20–25] However, the risk of ITP after childhood vaccines other than MMR is currently unknown.

Known rare severe complications of ITP include intracranial hemorrhage and severe bleeding.[26–29] Case reports and case series have described severe adverse events after MMR-associated ITP.[4,7,11,30] The risk of severe outcomes of ITP after MMR vaccination is thought to be quite low, but few studies have examined severe complications as an outcome.[9]

Using a large population from five managed care organizations, we sought to ascertain (1) the risk of ITP in children 6 weeks to 18 years of age after all vaccines routinely administered during childhood and (2) the risk of serious complications of ITP after vaccination in children.

METHODS

This investigation was conducted in five health care systems (Kaiser Permanente Colorado, Kaiser Permanente Hawaii, Kaiser Permanente Georgia, Kaiser Permanente Northern California, and Harvard Vanguard Medical Associates) by using data from the years 2000 to 2009, with Kaiser Permanente Colorado as the lead site. The study was a retrospective cohort study, with 1.8 million children enrolled in the cohort. We included children in the cohort who had been vaccinated while actively enrolled in their respective health plans. The institutional review board of each study site approved the study.

Ascertainment of Cases of ITP

Electronic Identification of Possible Cases

Initial identification of possible cases was conducted at the lead site by using electronic databases, with the analyst blinded to vaccination status. We reviewed the electronic data to exclude cases of thrombocytopenia from other known conditions by using the *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes (such as neonatal thrombocytopenia, aplastic anemia, disseminated intravascular coagulation, acquired hemolytic anemia, chronic liver disease, or malignancy). We then identified children $<$18 years of age with either two platelet counts of $<$50 000/μL in a 6-week period or one platelet count of $<$50 000/μL and an associated ICD-9 code of 287.0 to 287.9, inclusive, within 6 weeks of the low platelet count (see Appendix for specific ICD-9 codes).

Abstraction of Medical Records

For the remaining possible cases that were not excluded electronically, medical records were photocopied, deidentified at participating sites, and sent to the lead site. Trained medical abstractors blinded to vaccination status used a standardized paper-based instrument to collect the following: date of diagnosis, symptoms, platelet counts, date of resolution, exposure to medications, sequelae, treatment, medically attended illness within 6 weeks before ITP diagnosis, and medical setting of the diagnosis.

Confirmation of ITP Cases Using Medical Record Review

For the confirmatory chart review, a case was defined as a child aged 6 weeks to 18 years with a platelet count of $<$50 000/μL, with normal red and white blood cell indices, and the presence of clinical signs and symptoms of ITP, such as petechiae, significant bruising, or spontaneous bleeding. A case was excluded if, in the 6 weeks before diagnosis, the child was exposed to a platelet-depleting medication (such as antiepileptics and sulfonamide antibiotics) or infected with wild-type varicella or Epstein-Barr virus. Patients with no signs or symptoms of ITP, whose low platelet counts were found incidentally on complete blood count screening, were excluded. Children with probable sepsis or meningitis were also excluded. The ITP resolution date, determined by medical chart review, was defined as the date of the first platelet count of $>$100 000/μL with no evidence of a drop in platelet count in subsequent months. A case with no follow-up platelet count $>$100 000/μL was considered acute if there was other evidence in the medical record of ITP resolution. For this study, we defined chronic ITP as thrombocytopenia lasting $>$6 months, consistent with the definitions used in the literature at the time.[31,32] Since the time this study was designed and conducted, an expert panel has recommended a definition of chronic ITP as lasting $>$12 months[33]; this definition cannot be applied to the current study, because medical record abstraction information is not available for $>$12 months after the onset date. A pediatrician (S.T.O.) blinded to vaccination status independently reviewed all charts to confirm the onset date, assign case status, and assign the ITP resolution date.

"Serious adverse events" were defined as having any of the following: intracranial hemorrhage, bleeding requiring hospitalization, bleeding requiring transfusion of packed red blood cells or platelets, or death.

Analytic Methods

We used self-controlled case series (SCCS) methods to examine the risk of ITP after childhood vaccines. The SCCS method uses exposed and unexposed person-time to calculate incident rate ratios (IRRs) with each case acting as its own control.[34,35] Exposure in this context means exposure to a vaccine in a prespecified time window preceding the onset of ITP. The SCCS method has been shown to be a valid alternative to traditional cohort and case-control designs.[36]

For each child, follow-up time was limited to the 365 days before and after vaccination. We defined the exposed period as 1 to 42 days after vaccination for all vaccines. The unexposed period was defined as the time before and after the exposed period within 365 days of follow-up before or after vaccination. We compared the incidence of ITP during the 42 days after vaccination (exposed period) with the incidence of ITP during the unexposed period. Day 0 (the day of vaccination) was excluded, because any cases occurring at this time were most likely coincidental. Because a child with ITP cannot become a new case until the current illness resolves, patients diagnosed with ITP did not contribute person-time from the date of ITP onset to the date of resolution. For each vaccine, person-time was counted only during the age when the vaccine is licensed for use. For example, for MMR, person-time before 12 months of age did not contribute to the calculation.

For vaccines other than MMR and measles-mumps-rubella-varicella vaccine (MMRV), IRRs were calculated only when the other vaccines were not administered simultaneously with MMR or MMRV, because MMR has been highly associated with ITP in previous studies,[3–11] and the measles, mumps, and rubella components in MMRV are identical to those used in MMR. IRRs were calculated for each vaccine for the age groups shown in Table 2. Age groups were selected based on when the majority of each vaccine was given, with the exception of trivalent influenza vaccine (TIV), live attenuated influenza vaccine (LAIV), and Hep A, which are given over a broader age range. For varicella vaccine (VAR), 12 to 23 months was chosen instead of 12 to 19 months to be able to examine it separately from MMR, because most of the doses of VAR in the 12- to 19-month age group had been given simultaneously with MMR. The risk of ITP attributable to vaccine exposure was calculated as the difference between the incidence rates of exposed and unexposed children for each vaccine in the childhood series. For TIV and LAIV, exposures and case dates were limited to the September to December influenza vaccination season.

RESULTS

A total of 1.8 million children received a total of 15 million vaccine doses during the study period. Using electronic databases, among the 1.8 million children who received one or more vaccines, we identified 696 potential cases of ITP. Of these, we excluded 248 based on the presence of chronic conditions known to cause thrombocytopenia, leaving a total of 448 possible cases for chart review. After chart review, an additional 251 were excluded for the following reasons: alternative hematologic or oncologic diagnoses ($n = 94$), acute exclusionary illness such as probable sepsis or meningitis ($n = 46$), ITP in which an onset date could not be determined from the medical record ($n = 40$), medications known to cause ITP ($n = 28$), laboratory error ($n = 14$), ITP as an incidental finding ($n = 12$), completely missing medical records ($n = 10$), and recurrence of ITP ($n = 7$).

Cases of Immune Thrombocytopenic Purpura

Table 1 shows the characteristics of all chart-confirmed cases of ITP ($n = 197$). Cases were spread across all age ranges with similar numbers of cases among boys and girls. Most cases (93%) received hematology consultation, and half the children diagnosed with ITP had an acute illness in the previous 6 weeks. The majority of cases of ITP in younger children were classified as acute, whereas over one-third in the 11- to 17-year-old age group were chronic. Of 38 total cases exposed to vaccines in a 1- to 42-day risk window, 31 (81%) were acute, 6 (16%) were chronic, and 1 (3%) was unknown. Of 159 unexposed cases, 125 (79%) were acute, 31 (19%) were chronic, and 3 (2%) were unknown. All cases were included in the IRR calculations. There was no seasonal distribution of cases ($P = .94$).[37]

Risk of Immune Thrombocytopenic Purpura After Vaccines

The risk of ITP after vaccination by vaccine and age group is shown in Table 2. None of the routine childhood vaccines given in the first year of life was significantly associated with an increased risk of ITP. For vaccines routinely administered at 12 to 19 months of age, there was a significant association of ITP with MMR (IRR, 5.48, 95% confidence interval [CI] 1.61, 18.64). For other vaccines commonly given in this age range (VAR, diphtheria-tetanus-acellular pertussis vaccine [DTaP], pneumococcal conjugate vaccine [PCV], inactivated poliovirus vaccine [IPV], *Haemophilus influenza* type b vaccine [Hib], and HepA), there was no increased risk of ITP (calculated when not given simultaneously with MMR or MMRV). There

TABLE 1 Characteristics of Medical Record Validated Cases of Immune Thrombocytopenic Purpura (n = 197)

	Age Groups					Total
	6 wk to 11 mo	12–23 mo	24–59 mo	5–10 y	11–17 y	
Total ITP cases, n	17	30	63	55	32	197
Male, %	77	50	47	44	56	51
Platelet count at diagnosis in thousands/μL, mean	13	9	12	7	10	10
Hematology consultation, %	94	80	91	96	100	93
Nonexclusionary acute illness[a] within 6 wk before diagnosis, %	77	60	50	39	44	50
Nonexclusionary medication[b] within 6 wk before diagnosis, %	29	13	20	20	25	21
Nonexclusionary acute illness[a] at presentation, %	29	33	17	25	13	22
Diagnosis type, %						
Acute	94	83	8	80	59	79
Chronic	6	17	16	16	38	19
Unknown	0	0	2	4	3	2
For acute cases, mean time to resolution in days	22	21	45	41	36	36
Serious adverse events, %	0	0	2	5	6	3

ITP, immune thrombocytopenic purpura.

[a] Exclusionary acute illnesses included Epstein-Barr virus, varicella, sepsis/possible sepsis, bacteremia

[b] Exclusionary medications included sulfa drugs and antiepileptics such as valproic acid and carbamazepine; nonexclusionary medication means that the case was exposed to a medication, but that medication is not known to cause thrombocytopenia

were 1.9 cases of ITP per 100 000 doses of MMR.

The risk of ITP after Hep A, VAR, and tetanus-diphtheria-acellular pertussis vaccine (Tdap) was significantly elevated in three discrete age categories as shown in Table 2. For Hep A and Tdap, elevated IRRs were based on two vaccine-exposed cases, whereas, for VAR, there was one vaccine-exposed case.

Serious Adverse Events

Six of the 197 chart-reviewed cases of ITP had serious adverse events. All of the subjects with serious adverse events developed bleeding requiring hospitalization and/or transfusion, and none had any known long-term complications. There were no deaths. Of the 6 cases of serious adverse events, only one was a vaccine-exposed case, a 4-year-old girl who developed ITP complicated by hematochezia and hematuria requiring a packed red blood cell transfusion 4 weeks after receiving DTaP, MMR, and IPV.

Distribution of Cases

Figure 1 shows the distribution of cases by week in the risk period after vaccination for vaccines for which there were statistically significantly elevated IRRs during the exposed postvaccination period.

DISCUSSION

In this large multisite study of 1.8 million children, we examined the risk of ITP after all childhood vaccines. Our rate ratio estimates were based on medical chart-confirmed cases of ITP. We did not find an increased risk of ITP for any of the commonly given childhood vaccines other than MMR in younger children, an important finding given that the diagnosis of ITP is most common in the 1- to 3-year age group. We also present important new data showing an association of ITP with Hep A, Tdap, and VAR in older children. In addition, we provide data showing that serious sequelae after vaccine-associated ITP are rare, with only one child of 1.8 million vaccinated children having an event that required transfusion.

The negative findings from this study are important. In the 12- to 19-month age group (and 12–23 months for Hep A and VAR), age groups when ITP is relatively common, we found no increased risk of ITP for VAR, Hep A, DTaP, IPV, Hib, or PCV. The elevated IRR for MMRV in this age group is not surprising, because the measles, mumps, and rubella components in MMRV are essentially identical to MMR. The finding that the IRR for MMRV does not appear to be elevated beyond that of MMR is reassuring given the recently reported twofold increased risk of febrile seizures for MMRV compared with MMR and VAR given separately.[38] The confirmatory finding that MMR is associated with ITP helps validate the other findings of our current study, both positive and negative. While we found several elevated IRRs that approached statistical significance in older children, such as human papilloma virus vaccine (HPV), TIV, and meningococcal conjugate vaccine (MCV), estimates in older children are less stable because there are fewer cases of ITP on which to perform analyses.

The findings related to Hep A, Tdap, and VAR should be considered as hypothesis-generating rather than as conclusive evidence that these vaccines are associated with ITP. Our study used self-controlled case series analyses, an effective method for studying rare adverse events after vaccines.[34–36] However, the events in our analysis were very rare, and since we looked at many possible associations, there is the possibility that significant associations could surface by chance alone. This is particularly true in older children and adolescents. ITP is much more common in the 1- to 3-year age group than in infants $<$1 year or in persons $>$6 years of age.[39] Therefore, in the 1- to 3-year age groups, there are ample cases

TABLE 2 The Risk of Idiopathic Thrombocytopenic Purpura in the 1 to 42 Days After Vaccination, for Vaccines Routinely Administered During Childhood and Adolescence[a]

Vaccine (age group)	IRR	95% CI		*P*	Exposed Cases, *n*	Unexposed Cases, *n*
6 wk to 11 mo[2]						
Hib	0.53	0.14	1.94	.33	3	10
RV	—[b]	—	—	—	1	0
DTaP	—	—	—	—	0	7
IPV	—	—	—	—	0	7
HBV	—	—	—	—	0	7
PCV	0.58	0.15	2.18	.42	3	9
6 to 23 mo						
TIV	2.69	0.81	8.88	.11	5	7
12 to 19 mo						
MMR	5.48	1.61	18.64	.006	6	5
MMRV	2.87	0.78	10.56	.11	4	6
DTaP	1	0.21	4.81	.99	2	8
Hib	0.75	0.16	3.63	.72	2	9
HBV	—	—	—	—	0	2
PCV	0.72	0.14	3.97	.70	2	8
12 to 23 mo						
VAR	—	—	—	—	0	8
Hep A	0.22	0.03	1.82	.16	1	11
2 to 6 y						
TIV	1.86	0.41	8.38	.42	3	7
Hep A	1.14	0.34	3.86	.83	4	27
4 to 6 y						
MMR	3.06	0.42	22.30	.27	2	7
MMRV	—	—	—	—	0	5
VAR	4.39	0.46	41.65	.20	1	5
DTaP	2.57	0.53	12.37	.24	2	12
IPV	1.37	0.23	8.32	.73	2	12
7 to 17 y						
Hep A	23.14	3.59	149.30	.001	2	3
TIV	5.95	0.54	65.96	.15	2	2
11 to 17 y						
VAR	12.14	1.10	133.96	.04	1	2
MMR	—	—	—	—	0	1
HPV	9.71	0.87	108.92	.07	1	2
MCV	6.02	0.64	56.18	.12	1	4
Tdap	20.29	3.12	131.83	.002	2	3

[a] For vaccines other than MMR and MMRV, relative risks are shown only for vaccines when not given in conjunction with MMR or MMRV; LAIV is not shown, because there are no vaccine-exposed cases in any age category.

[b] Vaccines for which there are either no exposed or unexposed cases will have no IRR or CI reported.

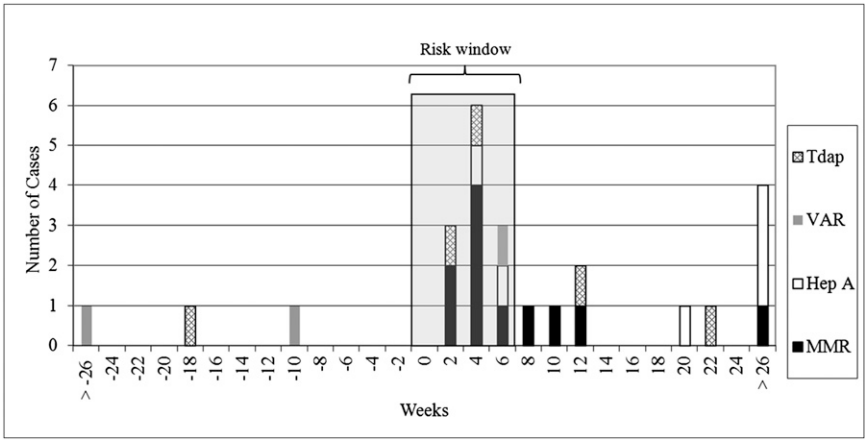

FIGURE 1
Distribution of cases of immune thrombocytopenic purpura, date of onset in relation to timing of receipt of vaccine (week 0), for vaccines with statistically significantly elevated incident rate ratios.

contributing person-time to both the exposed and unexposed denominators, creating more stable estimates of risk compared with older children where, because of the more pronounced rarity of ITP, there may be fewer cases contributing unexposed person-time. Regarding biologic plausibility, it is also unclear why these vaccines would trigger ITP in older age groups but not in younger ones. So, although it is important to consider that the findings showing an elevated risk of ITP after Hep A, VAR, and Tdap in older children may be real, these results must be interpreted with caution.

Reports of ITP in association with vaccines other than MMR are uncommon, and most previous information on ITP after vaccines other than MMR has come from vaccine adverse-event surveillance systems. Specifically relating to the findings in our present study of an increased risk with Hep A, Tdap, and VAR, there have been three published reports of ITP after whole-cell DTP vaccine[20,40] and one after DT vaccine,[40] but no published case reports of ITP after Hep A, VAR, or Tdap. Regarding cases of ITP reported from surveillance systems, as opposed to published case reports, a study from Canada based on an active surveillance system for vaccine adverse events reported 28 cases of ITP after DTP or DTaP vaccine compared with 77 reported after MMR, with only 10 reports after VAR (and no reports after Hep A, because children do not routinely receive Hep A in Canada).[41] In a recently published report from the US Vaccine Adverse Events Reporting System (VAERS), although there were 478 reports of ITP after MMR alone or in combination with other vaccines, there were 47 cases reported after VAR, 32 after Hep A, and only 8 after Tdap.[42] It is important to recognize that reports from surveillance systems are subject to reporting bias, and so providers may overreport

ITP after MMR because there is a known association.

The characteristics of our vaccine-associated ITP cases are important to consider. The vast majority of our cases were acute and mild. In addition, we had no vaccine-exposed cases that went on to develop serious permanent complications. Our findings are consistent with previous studies of vaccine-associated ITP in this regard. ITP after vaccination may have a similar clinical course as ITP from other causes. Studies on the genetics of ITP are ongoing, but it is thought that there is likely a genetic predisposition as in other immune-related diseases, such as insulin-dependent diabetes mellitus.[43]

There are several strengths and limitations in this study. It is the first study to examine in a systematic way the risk of ITP after vaccines other than MMR. In addition, the study was performed in a large network of managed care organizations with a large sample size and all cases were confirmed by medical record review. However, although the sample size was large, ITP is a rare disease; therefore, the number of confirmed ITP cases was relatively low. In addition, it is difficult to examine the risk of ITP after vaccines routinely given with MMR, a vaccine known to be associated with ITP. As discussed, the study was also limited by the methodologies currently available for examining rare adverse events.

Vaccine safety is a priority of national immunization policy, and studies designed to investigate vaccine adverse events are crucial to the ongoing success of our national immunization program. In our present study, we have used the best available science to help define the risk of a rare and usually benign vaccine adverse event, ITP, after all childhood vaccines. We found no increased risk for most of the vaccines in the childhood series, an unsurprising finding of an increased risk of ITP after MMR, and, less expected, we also found possible increased risk of ITP for Hep A, VAR, and Tdap in older children. Additional studies are needed to better explore these possible associations.

ACKNOWLEDGMENTS

This publication was supported by a subcontract from Kaiser Permanente with funds provided by the Food and Drug Administration. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of Kaiser Permanente or the Food and Drug Administration.

The authors thank Jo Ann Shoup at the Institute for Health Research at Kaiser Permanente Colorado and Melisa Rett, MPH, at the Harvard Pilgrim Health Care Institute for project management.

REFERENCES

1. Fisher OD, Kraszewski TM. Thrombocytopenic purpura following measles. *Arch Dis Child*. 1952;27(132):144–146
2. Oski FA, Naiman JL. Effect of live measles vaccine on the platelet count. *N Engl J Med*. 1966;275(7):352–356
3. Autret E, Jonville-Béra AP, Galy-Eyraud C, Hessel L. Thrombocytopenic purpura after isolated or combined vaccination against measles, mumps and rubella [in French]. *Therapie*. 1996;51(6):677–680
4. Beeler J, Varricchio F, Wise R. Thrombocytopenia after immunization with measles vaccines: review of the vaccine adverse events reporting system (1990 to 1994). *Pediatr Infect Dis J*. 1996;15(1):88–90
5. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol*. 2003;55(1):107–111
6. France EK, Glanz J, Xu S, et al; Vaccine Safety Datalink Team. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics*. 2008;121(3). Available at: www.pediatrics.org/cgi/content/full/121/3/e687
7. Jonville-Béra AP, Autret E, Galy-Eyraud C, Hessel L. Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional pharmacovigilance centres and Pasteur-Mérieux Sérums et Vaccins. *Pediatr Infect Dis J*. 1996;15(1):44–48
8. Kiefaber RW. Thrombocytopenic purpura after measles vaccination. *N Engl J Med*. 1981;305(4):225
9. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. *J Pediatr*. 2010;156(4):623–628
10. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child*. 2001;84(3):227–229
11. Nieminen U, Peltola H, Syrjälä MT, Mäkipernaa A, Kekomäki R. Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23 patients. *Acta Paediatr*. 1993;82(3):267–270
12. Hudson JB, Weinstein L, Chang TW. Thrombocytopenic purpura in measles. *J Pediatr*. 1956;48(1):48–56
13. Morse EE, Zinkham WH, Jackson DP. Thrombocytopenic purpura following rubella infection in children and adults. *Arch Intern Med*. 1966;117(4):573–579
14. Ozsoylu S, Kanra G, Savas G. Thrombocytopenic purpura related to rubella infection. *Pediatrics*. 1978;62(4):567–569
15. Polat A, Inan M, Cakaloz I, Karakus YT. A case of symptomatic idiopathic thrombocytopenic purpura during mumps. *Pediatr Hematol Oncol*. 2005;22(3):215–218
16. Rand M. Virus associated idiopathic thrombocytopenic purpura. *Transfus Sci*. 1998;19(3):253–259
17. Yeager A. Varicella associated thrombocytopenia: clues to the etiology of childhood idiopathic thrombocytopenic purpura. *Johns Hopkins Med J*. 1980;146:270–274
18. Yenicesu I, Yetgin S, Ozyürek E, Aslan D. Virus-associated immune thrombocytopenic purpura in childhood. *Pediatr Hematol Oncol*. 2002;19(6):433–437
19. Blanchette V, Bolton-Maggs P. Childhood immune thrombocytopenic purpura: diagnosis and management. *Hematol Oncol Clin North Am*. 2010;24(1):249–273
20. Arya LS, Ghai OP, Saraya AK. Thrombocytopenic purpura following DPT vaccination. *Pediatr Hematol Oncol*. 1993;10(4):381–383
21. Neau D, Bonnet F, Michaud M, et al. Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: retrospective study of seven cases. *Scand J Infect Dis*. 1998;30(2):115–118

22. Polat A, Akca H, Dagdeviren E. Severe thrombocytopenia after hepatitis B vaccine in an infant from Turkey. *Vaccine*. 2008;26(51):6495–6496
23. Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet*. 1994;344(8932):1293
24. Ronchi F, Cecchi P, Falcioni F, et al. Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child*. 1998;78(3):273–274
25. Sakha K, Malekian A, Aslandabadi S. Hepatitis B vaccination and infantile idiopathic thrombocytopenic purpura. *Med J Islam World Acad Sci*. 2005;15(4):149–151
26. Bolton-Maggs P. Severe bleeding in idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol*. 2003;25(suppl 1):S47–S51
27. Butros L. M.D., Bussel, J., M.D. Intracranial Hemorrhage in Immune Thrombocytopenic Purpura: A Retrospective Analysis. *J Pediatr Hematol Oncol*. 2003;25(8):661–664
28. Krivit W, Tate D, White JG, Robison LL. Idiopathic thrombocytopenic purpura and intracranial hemorrhage. *Pediatrics*. 1981;67(4):570–571
29. Woerner S, Abildgaard C, French BN. Intracranial hemorrhage in children with idiopathic thrombocytopenic purpura. *Pediatrics*. 1981;67(4):453–460
30. Jadavji T, Scheifele D, Halperin S; Canadian Paediatric Society/Health Cananda Immunization Monitoring Program. Thrombocytopenia after immunization of Canadian children, 1992 to 2001. *Pediatr Infect Dis J*. 2003;22(2):119–122
31. Blanchette V, Bolton-Maggs P. Childhood immune thrombocytopenic purpura: diagnosis and management. *Pediatr Clin North Am*. 2008;55(2):393–420, ix
32. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Pediatrics*. 2008;121(3). Available at: www.pediatrics.org/cgi/content/full/121/3/e506
33. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386–2393
34. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet*. 1995;345(8949):567–569
35. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768–1797
36. Glanz JM, McClure DL, Xu S, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. *J Clin Epidemiol*. 2006;59(8):808–818
37. Naus J, Wallenstein S. Temporal surveillance using scan statistics. *Stat Med*. 2006;25(2):311–324
38. Klein NP, Fireman B, Yih WK, et al; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e1
39. Yong M, Schoonen WM, Li L, et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. *Br J Haematol*. 2010;149(6):855–864
40. Bernheim M, Mouriquand C, Germain D, Gilly R, Nicolas A. 2 cases of prolonged thrombopenic purpura following an antidiphtheria-antitetanus vaccination. Splenectomy. Cure [in French]. *Pediatrie*. 1960;15:433–438
41. Sauvé LJ, Scheifele D. Do childhood vaccines cause thrombocytopenia? *Paediatr Child Health (Oxford)*. 2009;14(1):31–32
42. Woo EJ, Wise RP, Menschik D, et al. Thrombocytopenia after vaccination: case reports to the US Vaccine Adverse Event Reporting System, 1990-2008. *Vaccine*. 2011;29(6):1319–1323
43. Bergmann AK, Grace RF, Neufeld EJ. Genetic studies in pediatric ITP: outlook, feasibility, and requirements. *Ann Hematol*. 2010;89(suppl 1):S95–S103

(Continued from first page)

Address correspondence to Sean O'Leary, MD, MPH, Sections of Pediatric Infectious Diseases and General Academic Pediatrics, Children's Outcomes Research, Children's Hospital Colorado, Mail Stop F443, 13199 E. Montview Blvd, Suite 300, Aurora, CO 80045. E-mail: sean.o'leary@childrenscolorado.org

Portions of this work were presented at the National Immunization Conference, Washington, DC, March 28 to 31, 2011, and the Pediatric Academic Societies' Annual Meeting, Denver, Colorado, April 30 to May 3, 2011.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Dr Baxter receives research support from Sanofi Pasteur, GlaxoSmithKline, Novartis, Merck, and Pfizer. None of the other authors have any relevant disclosures.*

APPENDIX 1 *International Classification of Diseases, Ninth Revision* (ICD-9) Diagnosis Codes Used in Electronic Database Search

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

[a] Includes primary thrombocytopenia, unspecified (287.30), immune (idiopathic) thrombocytopenic purpura (ITP) (287.31), other primary thrombocytopenia (287.39) and congenital and hereditary thrombocytopenias.

[b] Includes thrombocytopenia caused by dilution, drugs, extracorporeal circulation of the blood, and platelet alloimmunization.

APPENDIX 2 Positive Predictive Value of *International Classification of Diseases, Ninth Revision* (ICD-9) Diagnosis Codes and Platelets Counts in Predicting a Confirmed Cases of Immune Thrombocytopenic Purpura upon Chart Review

Platelet Counts	Diagnosis Code Group	ITP Case		PPV, %
		Yes	No	
Years 2000–2004[a]				
1 count <50K and	287.31 ITP	0	0	—
1 count <50K and	Other TP code[b]	50	70	41.7
2 counts <50K and	No code	2	15	11.8
Total		52	85	38.0
Years 2005–2008				
1 count <50K and	287.31 ITP	90	24	78.9
1 count <50K and	Other TP code[b]	63	113	35.8
2 counts <50K and	No code	1	20	4.8
Total		154	157	49.5

PPV, positive predictive value; TP, thrombocytopenic purpura; ITP, immune thrombocytopenic purpura.

[a] Immune thrombocytopenic purpura (287.31) was not routinely used until 2005.

[b] 287, 287.0, 287.1, 287.2, 287.3 287.30, 287.39, 287.4, 287.5, 287.8, 287.9.

The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents

Sean T. O'Leary, Jason M. Glanz, David L. McClure, Aysha Akhtar, Matthew F. Daley, Cynthia Nakasato, Roger Baxter, Robert L. Davis, Hector S. Izurieta, Tracy A. Lieu and Robert Ball

Pediatrics originally published online January 9, 2012;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents

Sean T. O'Leary, Jason M. Glanz, David L. McClure, Aysha Akhtar, Matthew F. Daley, Cynthia Nakasato, Roger Baxter, Robert L. Davis, Hector S. Izurieta, Tracy A. Lieu and Robert Ball

Pediatrics originally published online January 9, 2012;