Thrombocytopenic Purpura after Measles-Mumps-Rubella Vaccination: A Systematic Review of the Literature and Guidance for Management

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Objective To determine the incidence of immune thrombocytopenic purpura (ITP) after measles-mumps-rubella (MMR) immunization compared with natural measles and rubella, its clinical course and outcome, and the risk of recurrence after repeat MMR vaccination.

Study design We performed a systematic review of the Ovid MEDLINE (1950 to present) bibliographic database. We selected studies that reported cases of thrombocytopenia in a known number of children who were immunized with MMR vaccine before development of ITP. We also extracted data from the same and other studies regarding bleeding manifestations and the resolution of MMR-associated thrombocytopenia or thrombocytopenic purpura within 6 months. Finally, we studied the risk of ITP recurrence after MMR immunization or reimmunization.

Results On the basis of 12 studies, the incidence of MMR-associated ITP ranged from 0.087 to 4 (median 2.6) cases per 100 000 vaccine doses. Severe bleeding manifestations were rare, and MMR-associated thrombocytopenia resolved within 6 months from diagnosis in 93% of the children. MMR vaccination of unimmunized patients with ITP and revaccination of patients with prior ITP did not lead to recurrence of thrombocytopenia.

Conclusions MMR-associated ITP is rare, self-limited, and non-life threatening, and susceptible children with ITP should be immunized with MMR at the recommended ages. *(J Pediatr 2010;156:623-8)*.

Surveillance of adverse reactions in recipients of vaccines indicates that the combined measles-mumps-rubella (MMR) vaccine, as well as the less frequently used monovalent live virus attenuated vaccines, can cause clinically apparent thrombocytopenia within 6 weeks after vaccination.[1] In a 1993 review of adverse events associated with childhood vaccines, the Vaccine Safety Committee of the Institute of Medicine concluded that a causal relationship exists between MMR vaccination and thrombocytopenia.[2] Although several case reports describe the occurrence of symptomatic thrombocytopenia after MMR vaccination,[3-14] no systematic review has been performed with the aim to determine the incidence of immune thrombocytopenic purpura (ITP) after MMR immunization and to study its clinical course, that is, bleeding manifestations and development of chronic thrombocytopenia. Moreover, although children with a history of thrombocytopenia may be at increased risk for development of thrombocytopenia after MMR vaccination, it is unclear how common ITP recurrences are after initial MMR vaccination or revaccination in such patients.

Because of limited data concerning the safety of MMR vaccination in patients with ITP, pediatricians, family practitioners, and hematologists who care for children with history of ITP may be reluctant to immunize or reimmunize these children with MMR, despite the fact that recent findings from the Centers for Disease Control and Prevention demonstrate that measles outbreaks can occur in communities with a high number of unvaccinated persons and that maintaining high overall MMR vaccination coverage rates in United States and elsewhere is needed to continue to limit the spread of measles.[15]

We performed a systematic review of the available medical literature to (1) calculate the incidence of ITP after MMR vaccination compared with natural infection with measles and rubella; (2) study the clinical course and outcome of MMR-associated ITP; and (3) estimate the risk of recurrence or worsening of the thrombocytopenia after initial MMR vaccination or revaccination in patients with history of non-vaccine– or MMR-associated ITP, as well as in patients with chronic ITP.

Methods

We searched the Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1950 to Present electronic bibliographic database on June 26, 2009, to identify articles that combined the terms measles or mumps or rubella or measles-mumps-rubella vaccine or the abbreviation "MMR" and thrombocytop(a)enia or thrombocytop(a)enic purpura with both the American and the British spelling for these terms. Additionally, we hand-searched the bibliographic references of relevant studies for additional publications that were

ITP	Immune thrombocytopenic purpura
MMR	Measles-mumps-rubella vaccine

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Table I. Table showing the limitations set (line 1), the number of articles removed in each step (line 2) and the flow of articles (line 3)

Line 1		A: Duplicates	B: Limit to English, human and children (ie, 0-18 years old)	C: Case reports excluded	D: Non-eligible* journal articles (n = 35) and reviews (n = 6)	E: Additional non-eligible letters (n = 1), guidelines (n = 2), reviews/meta-analyses (n = 3), comparative studies (n = 1), clinical trials (n = 1), and journal articles (n = 5)
Line 2	Number of articles removed	4	102	41	41	13*
Line 3	210⇒⇒⇒	206⇒⇒⇒⇒⇒	104⇒⇒⇒⇒⇒⇒	63⇒⇒⇒⇒⇒	22⇒⇒⇒⇒⇒⇒	9

Non-eligible, Not providing incidence data for MMR-associated ITP.
Three additional eligible studies were identified from the references of the 9 identified eligible articles.
*Two of the 13 articles that were eliminated in this step were eligible for the second study objective, i.e., for the study of the clinical course and outcome of MMR-associated ITP.

missed in the initial search strategy. Finally, using the Scopus abstract and citation database of research literature, we searched the citations of the eligible articles for the same purpose. This strategy was run independently by 2 authors (E.M. and E.F.). The detailed search strategy is explained in **Table I**.

"MMR-associated ITP" was defined both a platelet count <150 000/mm^3 and confirmation of thrombocytopenia by blood smear examination or the presence of clinical signs and symptoms of spontaneous bleeding, according to the Brighton Collaboration Thrombocytopenia Working Group criteria in an individual vaccinated with MMR.[16] Although the risk of thrombocytopenia after MMR vaccine is higher within the first 6 weeks after immunization, we did not limit our search on the basis of this time frame but included all studies that reported on what was judged by the authors to be MMR-associated ITP.

To calculate the incidence of MMR-associated ITP expressed per 100 000 vaccine doses, those studies were eligible only if cases of MMR-associated thrombocytopenia were reported in relation to the number of administered vaccine doses or which contained data allowing for an incidence to be calculated. To compare the incidence of MMR-associated ITP with that of the corresponding natural infections, we also searched for articles that provided data regarding the incidence of thrombocytopenia after natural measles and rubella infections, because these 2 viruses are regarded as the main causes of thrombocytopenia in the MMR vaccine.

To study the clinical course and outcome of MMR-associated ITP, after the identification of studies that provided an incidence of MMR-associated ITP and of additional studies on MMR-associated ITP, we extracted data regarding the platelet count, a valuable but surrogate end-point of ITP, the interval after vaccination within which thrombocytopenia resolved, bleeding manifestations or other complications and development of chronic ITP. Because traditionally, chronic ITP is defined as disease that persists for >6 months after diagnosis, we used this time point to define the percentage of patients in whom the platelet count had normalized. If such information was unavailable, we used other relevant clinical data (eg, bleeding manifestations or authors' statements that resolution occurred, even if the exact time-point of platelet normalization was not described) to assess the outcome of MMR-associated ITP.

To evaluate the risk of recurrence or exacerbation of ITP (either non-vaccine– or vaccine-associated) after MMR immunization (primary or booster), we searched for studies excluding case reports that described administration of the MMR vaccine in patients with acute or chronic ITP after MMR vaccination or revaccination. Editorials, letters, narrative reviews, meta-analyses/reviews, guidelines, and journal articles that did not provide data relevant to our objectives were excluded. Non-English articles were also excluded; however, this was done after studying their English abstracts to avoid missing potentially eligible articles.

Results

Our initial search identified 206 potentially eligible publications. By applying the combined limits of English-only articles, humans, and children 0-18 years old, an additional 103 articles were automatically removed. However, manual search revealed 1 of them to be eligible. After removing 41 case reports, 36 journal articles, and 5 reviews that contained no data on MMR-associated ITP, the number of potentially eligible studies was limited to 22. A total of 13 additional studies were removed because they did not provide data on the incidence or the clinical course of MMR-associated ITP, limiting the number of eligible studies to 9.[17-25] Finally, by reviewing the bibliographic references of these articles, we found 3 additional eligible articles[26-28]; hence, raising the total number of evaluable studies to 12. On the date of our search, these studies had been cited 276 times. Identification and screening of these citations did not reveal any additional eligible studies.

The 12 eligible studies were conducted in Canada, Denmark, Finland, France, Germany, Japan, Sweden, United Kingdom (n = 3), United States, and the Nordic countries. As shown in **Table II**, the method of surveillance to capture thrombocytopenia or thrombocytopenic purpura, as a side effect of MMR vaccination was different among various countries (ie, active surveillance, passive surveillance, or linkage of children hospitalized for ITP to immunization data). The reported incidence of MMR-associated ITP ranged

Table II. Eligible studies that provide an incidence of MMR-associated ITP listed by year of publication

Country	Author [publication year]	Study method	Time frame for MMR-associated ITP (stated or inferred from the results)	Incidence of MMR-associated thrombocytopenia
Canada	Koch et al[26] [1983]	Passive surveillance	Not stated	1/100 000
Sweden	Bottiger et al[27] [1987]	Active surveillance	Not stated	2.7/100 000
Germany	Fescharek et al[28] [1990]	Passive surveillance	Not stated	0.2/100 000
Finland	Nieminen et al[18] [1993]	Active surveillance	Not stated but last patient accrued within 60 days after MMR vaccination	3.33/100 000
United Kingdom	Farrington et al[19] [1995]	Linkage of children hospitalized for ITP to immunization data	Within 35 days after MMR vaccination	3.44/100 000
France	Jonville-Béra et al[20] [1996]	Passive surveillance (retrospective study of spontaneous case reports)	Within 45 days after MMR vaccination	0.95/100 000
Denmark	Pedersen-Bjergaard et al[17] [1996]	Passive surveillance (retrospective study of spontaneous case reports)	Not stated	0.88/100 000
United Kingdom	Miller et al[21] [2001]	Linkage of children hospitalized for ITP to immunization data	Within 42 days after MMR vaccination	3.1/100 000
United Kingdom	Black et al[22] [2003]	Nested case-control study	Up to 26 weeks after MMR vaccination	4/100 000
Nordic countries	Rajantie et al[23] [2007]	Active prospective surveillance	Within 1 month after MMR vaccination	3.33/100 000
Japan	Nakayama et al[25] [2007]	Passive surveillance	Not stated	0.087/100 000
USA	France et al[24] [2008]	Modified cohort design	Within 42 days after MMR vaccination	2.5/100 000

from 0.087/100 000 in Japan over the period 1994-2004 to 4/100 000 MMR doses in United Kingdom during 1988-1999 (a 46-fold difference; median incidence 2.6/100 000 doses). However, 7 of 12 studies reported a narrower range of incidence of MMR-associated ITP between 2.5/100 000 and 4/100 000 doses (a 1.6-fold difference). Regarding the incidence of thrombocytopenia after natural infection, we identified 4 relevant studies, 1 dealing with measles and 3 with rubella infections.[29-32] On the basis of 30 000 school-aged children infected during a 1963–1964 measles epidemic in 1 Pennsylvania county, 10 children had development of ITP, giving an incidence of measles-associated ITP of 33/100 000 children.[29] In another report, among 16,441 rubella cases reported in 1958, 1 child developed symptomatic ITP, giving an incidence of ITP after natural rubella infection of 6/100 000 cases.[30] In a 1965 Baltimore City Health Department report, 14 cases of thrombocytopenia were reported among 1183 cases of natural rubella infection, giving an extremely high incidence of rubella-associated ITP of approximately 1200 per 100 000 cases.[31] Finally, during a 1976–1977 rubella epidemic in southern Japan, among 14 322 clinical rubella cases, 9 patients had development of purpura, yielding an incidence of rubella-associated ITP of 63/100 000 cases.[32]

The clinical course and outcome of MMR-associated ITP was described in 7 of the 12 eligible studies of calculation of an incidence of MMR-associated ITP and in 2 additional studies [33,34] (**Table III**). Remarkably, none of these 9 eligible studies reported in sufficient details the clinical course of MMR-associated ITP. In 5 of them, the MMR-associated thrombocytopenia resolved within 6 months from diagnosis in 90-95.8% of the affected children.[18,20,23,24,33] In the study by Miller et al,[21] although the resolution rate of thrombocytopenia at 6 months was unclear, the authors provided evidence that MMR-associated ITP was more self-limited compared with the non-vaccine–associated ITP. More specifically, the length of initial hospital admission was less (3 vs 5 days) and the platelet count at presentation was higher (>20 000/mm^3 in 33% vs 19% of patients) in the vaccine-associated cases.[21] Finally, in the study by Fescharek et al, all 11 reported patients with MMR-associated ITP had a benign course, and the platelet counts returned to normal, although it is unclear when this recovery occurred.[28] Five children had development of gastrointestinal hemorrhage (2 of them required a blood transfusion),[18,20,34] 3 additional patients required a blood transfusion (no additional details provided),[23] 1 child had development of pulmonary hemorrhage,[34] 1 had development of hematuria[20] and 1 required splenectomy.[34] One boy died of intracranial hemorrhage, but the bleeding occurred after a closed head injury caused by a fall.[33]

Only 6 publications reported the risk of recurrence of thrombocytopenia after MMR vaccination in children with ITP, either non-vaccine– or MMR-associated ITP (**Table IV**).[21-24,35,36] Among 131 children with a history of ITP (non-vaccine–associated in 94, MMR-associated in 26, and other-vaccine associated in 11 children), none had a recurrence of ITP within 6 weeks after the first or second dose of MMR.[21-24,35] Finally, a case series of 3 patients with chronic ITP reported no worsening of thrombocytopenia after MMR immunization.[36]

Discussion

Our first goal was to calculate the incidence of thrombocytopenia after MMR vaccination compared with that after

Table III. Clinical course of patients with MMR-associated ITP

Author	Number of patients with MMR-associated ITP	Percent (absolute number) of patients with resolution of thrombocytopenia at ≥ 6 months	Other markers of severity of ITP other than resolution at 6 months
Nieminen et al[18]	23	95.7% (22)	1/23 patients required a blood transfusion for intestinal bleeding
Jonville-Béra et al[20]	57*	91.2%† (52)	3/57 patients had development of intestinal bleeding and 1/57 had hematuria
Miller et al[21]	9	Not given	Decreased length of admission and higher platelet count at diagnosis in patients with MMR-associated ITP compared with non-vaccine ITP
Black et al[22]	52	Not given	No serious complications reported
Rajantie et al[23]	24	95.8% (23)	3/24 (12.5%) patients needed a transfusion
France et al[24]	20	90% (18)	—
Fescharek R et al[28]	11	Not given	100% of the patients recovered
Jadavji et al[33]	48	93.8%‡ (45)	1 child died of intracranial hemorrhage (subdural hematoma) after a closed head injury caused by a fall
Beeler et al[34]	55	Not given	1 patient required a blood transfusion for intestinal bleeding 1 patient had development of pulmonary hemorrhage 1 patient had a splenectomy
Overall	299	93% (160/172 with follow-up data)	—

*Twelve patients received bivalent measles-rubella vaccine, 4 received rubella and 2 measles monovalent vaccines.
†The resolution of thrombocytopenia was achieved within 6 weeks.
‡Forty-six of 48 patients received MMR, 2 received measles monovalent vaccine. Three of 48 (6.25%) patients had development of chronic thrombocytopenia defined as thrombocytopenia for >3 months after diagnosis.

measles and rubella. The chance of developing ITP after MMR vaccination is approximately 2.6/100 000 vaccine doses (median value, range 0.087 to 4/100 000).[17-28] The risk of thrombocytopenia after natural measles or rubella is several fold higher ranging from 6 to 1200/100 000 cases.[29-32] Remarkably, there is no overlap in the incidence figures between MMR-associated and measles or rubella-induced thrombocytopenia, that is, even the highest incidence (4/100 000 vaccine doses) reported for MMR-associated ITP[22] is 50% lower than the lowest reported incidence of rubella-associated thrombocytopenia (6/100 000 cases).[30]

As shown in Table II, countries or regions with active surveillance systems for vaccine-associated side effects report higher incidence rates of MMR-associated ITP compared with countries with passive surveillance systems, suggesting that the observed differences may be, to some extent, the result of different surveillance methods used rather than the result of "true" differences in the incidence of MMR-related thrombocytopenia and thrombocytopenic purpura. Nevertheless, 7 of 11 studies reported similar incidence rates ranging from 2.5 to 4/100 000 vaccine doses. The actual incidence of MMR-associated thrombocytopenia is impossible to ascertain precisely because children with mild or moderate thrombocytopenia are unlikely to have bleeding symptoms and, hence, are not likely to come to medical attention.[11]

The second goal of our study was to assess the outcome of patients who had development of ITP shortly after MMR immunization. As shown by our review on the basis of 172 patients with follow-up data, 93% of children with MMR-associated ITP recovered within 6 months from diagnosis.[18,20,23,24,33] Hence, only 7% had development of chronic disease, whereas according to Intercontinental Cooperative ITP Study Group data, chronic disease develops in approximately 28% of children with ITP 12 months to 10 years of

Table IV. Safety of MMR vaccination or revaccination in children with history of MMR-associated or non-vaccine–associated ITP

Study	Number of patients, type of ITP	ITP recurrences after MMR vaccine
Miller et al[21]	21 patients, non-vaccine–associated ITP	0/21 after 1st MMR vaccine dose
Black et al[22]	2 patients, MMR-associated ITP	0/2 after 2nd MMR vaccine dose
Black et al[22]	9 children, non-vaccine–associated ITP	0/7 after 1st MMR vaccine dose
France et al[24]	31 children, non-vaccine–associated ITP	0/31 after 1st MMR vaccine dose
Stowe et al[35]	33 children, non-vaccine–associated ITP	0/33 after 2nd MMR vaccine dose
Bibby et al[36]	3 children, chronic non-vaccine–associated ITP	0/3 after 1st MMR vaccine dose*
Rajantie et al[23]	24 children, MMR-associated ITP	0/24 after 2nd MMR vaccine dose
Rajantie et al[23]	11 children, other vaccine-associated ITP	0/11 after 2nd MMR vaccine dose

*The first of the 3 patients received 2 doses of MMR vaccine.

age.[37] Similarly, the Nordic ITP Working Group has estimated that approximately 25% of children with ITP have development of chronic disease.[38,39] Thus MMR-associated ITP is less likely to become chronic compared with the more common non-vaccine– associated disease. However, the percentage of children who have development of chronic non-vaccine–associated ITP appears similar to that of MMR-related cases in children aged 12 to 18 months of age alone. More specifically, in the study by France et al[24] among children with ITP unexposed to MMR aged 12 to 23 months, only 3 of 43 (7%) had development of chronic ITP versus 2 of 20 (10%) of those with MMR-associated ITP. Moreover, it is estimated that at least 70% to 75% of ITP cases in children aged 12 to 18 months of age are believed to be related to MMR.[24]

As shown in **Table III**, the bleeding manifestations of MMR-associated ITP usually are self-limited and not life-threatening. Serious bleeding requiring blood transfusion occurs rarely. One case of lethal intracranial hemorrhage was not spontaneous but was related to a closed head injury.[33] To the best of our knowledge, there are no cases of spontaneous fatal bleeding caused by MMR-related thrombocytopenia, and deaths from bleeding have been reported in patients with rubella-associated thrombocytopenic purpura.[40-42]

On the basis of the study by France et al[24] and the annual US birth cohort, it has been estimated that approximately 100 cases of ITP per year can be attributed to the MMR vaccine in United States.[43] Because the reported incidence of ITP is 4 to 5.3/100 000 children[44,45] and the population of the United States includes approximately 80 million children, 2.3% to 3.1% of the 3200 to 4240 annual cases of childhood ITP in the United States are MMR-associated. However, this relatively low percentage does not pertain to children aged 12 to 18 months alone. Interestingly, among 433 cases of ITP diagnosed in Denmark over the period 1959–1969 in children $\leq$ 15 years of age, 61 (14%) were due to natural rubella (n = 42), measles (n = 14), or mumps (n = 5) infection.[46] Hence, natural infections caused by any of the viruses contained in the MMR vaccine currently have become an infrequent cause of ITP.

The third goal of our systematic review was to search for studies on the safety (ie, risk of thrombocytopenia recurrence or worsening) of MMR vaccination or revaccination in children with either non-vaccine– or MMR-associated ITP. Only 6 such reports were found,[21-24,35,36] partially because most children (>90% to 95%), if tested, will be immune after 1 dose of MMR, necessitating the administration of a second dose in very few susceptible children with ITP. Four studies showed that children with history of known non-vaccine–associated ITP in remission who had previously received a first dose of MMR vaccine did not have a recurrence within 6 weeks after vaccination.[21,22,24,35] Two studies, 1 with only 2 and another with 24 children with MMR-associated ITP, showed no recurrences[13] after the second MMR dose.[22,23] Regarding the safety of MMR vaccination in patients with chronic ITP, there are no firm data.[36]

Our systematic review has several limitations. First, we excluded non-English articles. However, by studying English abstracts of these studies, we do not believe that we missed any studies that included data relevant to our goals. Second, we may have underestimated thrombocytopenia as a side effect of MMR vaccine, because in no studies was routine surveillance blood counts performed within the first few weeks after vaccination. Third, we excluded case reports. The reason for this exclusion is that case reports describing a recurrence of ITP after MMR vaccination of a child with history of MMR-related or idiopathic ITP are more likely to be published than those describing children with history of ITP and no recurrence of thrombocytopenia after vaccination. Hence, there is an inherent danger for bias. Finally, although all authors of this study are frequently consulted by practitioners about MMR vaccination for children with history of ITP, we have no data to prove that appropriate immunizations are avoided in these children. However, given their physicians' need for such consultations, this is likely to be the case.

The decision to administer MMR vaccine to children with history of ITP should be based on assessment of immunity after the first MMR dose and the benefits of protection against the 3 viruses in the vaccine compared with the risks of recurrence of thrombocytopenia after immunization.[47] Because of the much higher likelihood of thrombocytopenia after natural infection, the benefits of vaccination greatly exceed the risks of severe symptomatic thrombocytopenia caused by immunization. Hence, children who have development of ITP within 6 weeks of their first MMR dose should have antibody tests performed. If the child is immune, repeat immunization is not necessary. If the child is not immune (a 5% to 10% chance), we recommend a second dose of MMR. We also recommend that children with known ITP not yet immunized against measles, mumps, and rubella or with no evidence of adequate immunity despite prior immunization should be immunized at the recommended ages provided that intravenous immunoglobulin therapy has not been given within 8 to 11 months.[47] ■

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