Illness after measles–mumps–rubella vaccination

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Objectives: To provide accurate information on the common sequelae of measles–mumps–rubella (MMR) vaccination and to compare postvaccine symptoms in children vaccinated at 13 and 15 months.
Design: Prospective cluster randomized controlled trial.
Setting: Twenty-two family practices in southwestern Ontario.
Patients: All 376 infants who were due to receive MMR vaccine in the next year; 253 (67.3%) successfully completed the study.
Intervention: MMR vaccine administered at 13 months by half of the family physicians and at 15 months by the remaining half.
Outcome measures: Family physician's physical findings in children 7 days and 30 days after vaccine; reported illnesses by mothers in a daily diary in the month before and after vaccination and medical records of visits to family physicians and hospital admissions in the month before and after vaccination.
Results: Compared with the incidence rates in the corresponding weeks before vaccination, the rates of lymphadenopathy (23.8%) and fever (16.8%) were higher 1 week afterward and the rate of rash (26.9%) was higher 7 to 14 days afterward. Fewer health problems were reported in the third and fourth weeks after vaccination than in the corresponding weeks beforehand. Hospital admissions after vaccination were no more frequent than those before once cause and time of admission were taken into account. The two age groups did not differ in any of the outcomes.
Conclusions: Mothers should be informed about the possibility of increased physical findings in the weeks after MMR vaccination, especially lymphadenopathy, nasal discharge and rash. Since the occurrence of sequelae does not seem to differ significantly between 13-month-old recipients and 15-month-old recipients, it should not influence the decision of when to administer the vaccine.

Objectifs : Renseigner de façon précise sur les suites courantes de la vaccination rougeole–oreillons–rubéole (ROR) et comparer les symptômes après la vaccination chez les enfants vaccinés à 13 et à 15 mois.
Conception : Étude clinique prospective randomisée et contrôlée et en grappes.
Contexte : Vingt-deux cliniques de médecine familiale du sud-ouest de l'Ontario.
Patients : Les 376 enfants qui devaient recevoir leur vaccin ROR au cours de l'année; l'étude complète a porté sur 253 (67,3 %) des sujets.
Intervention : La moitié des médecins a administré le vaccin ROR à 13 mois et l'autre à 15 mois.
Mesures des résultats : Symptômes physiques observés par les médecins de famille chez les enfants de 7 à 30 jours après la vaccination; maladies notées par les mères dans un carnet, sur une période allant d'un mois avant à un mois après la vaccination, et visites au médecin de famille et admissions hospitalières consignées aux dossiers médicaux pour la même période.
Résultats : Par comparaison avec le taux d'incidence au cours des semaines correspondantes

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précédant la vaccination, on a constaté une augmentation d'adénopathie (22,5 %) et de fièvre (16,8 %) une semaine après, et de d'éruptions cutanées (26,9 %) de 7 à 14 jours après. On a signalé moins de problèmes de santé au cours des troisième et quatrième semaines après la vaccination qu'au cours des semaines correspondantes avant la vaccination. Il n'y avait pas plus d'admissions hospitalières après qu'avant la vaccination, une fois pris en compte les causes et le moment de l'admission. Il n'y avait pas de différence de résultats entre les deux groupes d'âge.

Conclusions : On devrait informer les mères de la possibilité que des symptômes physiques se manifestent en plus grand nombre pendant les semaines suivant la vaccination ROR, particulièrement l'adénopathie, l'écoulement nasal et les éruptions cutanées. L'âge ne devrait pas influencer la décision de vacciner, puisqu'il ne semble pas y avoir de différence symptomatique sensible chez les receveurs de 13 et de 15 mois.

There has been a significant increase in the number of measles outbreaks in the United States and Canada over the past 10 years.[1,2] This may be due to inadequate vaccination coverage, an issue causing considerable concern,[3] or to the improper timing of vaccination. Recommendations that guidelines be developed for health care professionals have been made so that information on the measles–mumps–rubella (MMR) vaccine, with its concomitant risks and benefits, can be provided to patients or their parents.[4,5] However, the common sequelae of MMR vaccination are not well known and may lead to unnecessary treatment.[6]

The purpose of this study was to (a) provide accurate information on the common sequelae of MMR vaccination and (b) compare postvaccine symptoms in children vaccinated at 13 and 15 months.

The existing information on adverse effects of MMR vaccine in Canada comes from the manufacturer's list of such effects obtained through premarketing studies,[7] a study of a recently introduced MMR vaccine (Trivirix)[8] and two retrospective family-practice-based studies.[9,10] However, all of these studies have limitations: the manufacturer's list included occurrences of unspecified frequency, the Trivirix study relied on a single examination by a nurse 10 days after vaccination and did not specify the criteria for an adverse reaction, and the retrospective studies included only problems sufficiently serious in the parent's mind to bring the child back to the doctor's office.

The possible adverse effects listed by the manufacturer are malaise, sore throat, headache, fever, rash, erythema, induration, regional lymphadenopathy, parotitis, orchitis, thrombocytopenia and purpura. Allergic reactions such as urticaria, arthritis, arthralgia and polyneuritis have also been reported. Encephalitis is reported to occur in one case per million doses of all live vaccines administered, 1000 times less frequent than the incidence of encephalitis with natural measles infection.[7] The Trivirix study found that the principal problems after vaccination were tonsillitis (in 56.7% of cases), cervical adenopathy (in 43.3%) and parotitis (in 20%).[8] The retrospective studies showed an increase in the number of physician visits for conjunctivitis, otitis media and upper and lower respiratory tract infections.[9,10]

A double-blind placebo-controlled crossover study of reactions to MMR vaccine in 581 pairs of twins was conducted in Finland.[11] The incidence rates of symptoms such as cough, runny nose, nausea and vomiting, recorded by the mothers over 1 month after vaccination, were lower in the vaccinated group than in the placebo group after the second week; this suggests a "protective effect" of the vaccine, perhaps owing to the induction of interferon. Because of the involvement of twins in that trial, subtraction of the incidence of a given symptom in the twin receiving the placebo from the incidence of the same symptom in the vaccinated twin revealed a true adverse reaction rate for each of 15 signs and symptoms. These rates were much lower than generally reported. The authors attributed this to the frequent occurrence of symptoms in children in general and suggested that MMR vaccine is safer than currently recognized. The study had the weakness of relying only on the observations of the mothers; the investigators were unable to comment on the incidence of otitis media, tonsillitis and lymphadenopathy, which require the examination by an objective, medically trained observer.

Our second goal, to compare postvaccine illnesses in children vaccinated at different ages, will add to the debate about the optimum time to vaccinate children. The manufacturer and the National Advisory Committee on Immunization recommend vaccination after 12 months to avoid interference with the immunogenic response by maternal antibodies.[7,12] However, other authorities have asked that the vaccine not be given until 15 months, because 12-month-old recipients had a lower seroconversion rate than 15-month-old recipients.[2] The attack rate in measles outbreaks in the United States and Canada has been two to three times higher in children vaccinated at 12 to 13 months of age than in those vaccinated at 15 months.[13]

Methods

The study was conducted by 22 family physicians in Oxford and Middlesex counties and the Waterloo region of southwestern Ontario. The design was a prospective cluster randomized controlled study in which half of the family physicians were randomly assigned to administer the MMR vaccine (M–M–R II; Merck Sharp & Dohme Canada, Kirkland, Que.) at 13 months and the

other half at 15 months. Thirteen months was chosen instead of 12 months to ensure that vaccination occurred after the twelfth month, to comply with current recommendations. All babies were identified in each practice who were due to receive MMR vaccine in the next year. The mothers were asked to consent to the study and to visit the doctor's office 1 month before vaccination.

The data on illnesses were collected from three sources: (a) results of examination by the family physician of each child at vaccination and 7 and 30 days afterward, (b) a standardized close-ended diary kept daily by each mother for the 4 weeks before and the 4 weeks after vaccination and (c) medical records of the family physicians indicating any illness resulting in patient-initiated visit or admission to hospital during the month before and the month after vaccination.

Family physician's examination

At each of the three study visits to the physician's office the following were examined and any positive findings noted: eyes (conjunctiva); ears (tympanic membranes, particularly for light reflex, retraction, radial erythema, inflammation and bulging); mouth (for enanthema and Koplik's spots) and throat (tonsils and parotid gland); anterior triangle and posterior triangle, including postauricular nodes and occipital nodes (for signs of lymphadenopathy); lungs (for rales or rhonchi); abdomen (for tenderness and signs of organic disease); genitourinary tract (for testicular swelling); central nervous system (for alertness); skin (for rash, erythema, macules, papules and vesicules); and temperature.

Physicians attended two workshops to ensure consistency in the criteria for positive findings. No formal assessment was made of the interobserver agreement. However, the same physician examined a child on each of the three occasions, and each physician entered approximately equal numbers of children into the study. These strategies were implemented to reduce interobserver bias.

Symptom diary

The daily diary was designed to overcome problems of recall, which hamper alternative methods such as weekly and monthly interviews.[14–16] It was pilot tested for clarity and mothers' compliance. The diary included the following four questions, with responses recorded on a 5-point scale (1 poor, 3 average, 5 good).

- What sort of day has this been for your child?
- How do you rate your child's eating today?
- How do you rate your child's sleeping pattern today?
- Did your child have any health problems today? If Yes, did you (a) talk with a friend or relative, (b) use over-the-counter medicine or (c) use medicine prescribed by doctors? Were the following problems bothering your child today: rash, swollen glands, runny nose, runny eyes, cold sores, cough, sore throat, fever?

Two variables reflecting the child's illness were created from the daily diary. First, the variable *days with health problems* was ascertained from the responses to the question Did your child have any health problems today? Second, each day in the month before and the month after vaccination was classified as to whether or not the child was sick. The variable *sick day* referred to a day during which the mother identified a health problem as a symptom rather than some other concern (e.g., ingoing foot) and during which at least one of the following applied: a poorer eating or sleeping rating than that for the previous day, or the use of medications (over the counter or prescribed).

The number of days with health problems and the number of sick days in each of the 4 weeks after vaccination were compared between the two groups of children. The unpaired t-test was used to compare differences. The statistical power of the study to detect a difference of 2 sick days between the 13-month and 15-month age groups, at an α value of 0.05, was 0.80. To compare illness rates before and after vaccination we conducted paired t-tests on the number of days with health problems per week for the corresponding weeks before and after vaccination.

Results

There were 376 eligible children, of whom 253 (67.3%) successfully completed the study (this included their mother keeping the diary for the 2 months and the necessary follow-up appointments). Of the 123 remaining children 45 had mothers who refused to participate, 24 were taken out out of the study, 23 were not included in the results because of incomplete data (e.g., a diary with more than 14 days missing or a missed visit on day 7), and 31 were missed or already had received the vaccine.

Of the 253 children who completed the study 126 were randomly assigned to be vaccinated at 13 months and 127 at 15 months. Some vaccinations were delayed as much as a week to allow a child to recover from an illness. Boys represented 55.4% of the total number of children. This proportion did not differ significantly between the two groups; nor did birth weight, gestational age at birth, weight at vaccination, mother's age, mother's educational level, child-care arrangements, number of preschool and school-aged children in the household, birth order and number of hours in child care. The father's educational level was significantly higher in the 15-month group than in the 13-month group; this likely reflected the cluster randomized design, in which similar parents would choose the same physician, and was not thought to significantly differentiate the two groups of children.

Illness after vaccination

The number of days with health problems did not differ significantly between the two age groups (Table 1). Overall, the children had a health problem approximately 2 days each week (Table 1). Also not significantly different between the two groups were the number of sick days and the physical findings at examination 7 days after vaccination. Both groups exhibited on average close to one positive finding per child (0.89 in the 13-month group and 0.93 in the 15-month group).

The medical records indicated that the number of visits on average to the family physician in the month after vaccination (omitting the visit at 7 days required by the study) did not differ significantly between the 13-month group and the 15-month group (0.75 v. 0.79 respectively).

Six children were admitted to hospital. Four in the 13-month group were admitted because of dehydration, earache and fever (on day 19), pneumonia (on day 25), dehydration, diarrhea and anorexia (on day 25) and burns (on day 28); two in the 15-month group were admitted because of fever, anorexia and bruising (on day 10) and red throat, fever and leukocytes in urine (on day 11). The case of fever, anorexia and bruising was diagnosed as immune thrombocytopenia, which has previously been reported after vaccination.[17-21] In this case the symptoms became apparent 5 days after vaccination.[22]

Table 1: Number of days with health problems reported in daily diaries for children given measles–mumps–rubella (MMR) vaccine at 13 and 15 months

Week after vaccination	Age group; mean duration of health problems, d*	
	13 mo	15 mo
First	2.1 (n = 120)	2.1 (n = 122)
Second	2.6 (n = 122)	2.4 (n = 124)
Third	2.1 (n = 124)	2.0 (n = 122)
Fourth	1.9 (n = 109)	2.1 (n = 110)

*The number of mothers who completed the diary for each of the 7 days varied slightly from week to week.

Illness before and after vaccination

Unexpectedly, the mean number of days with reported health problems was not significantly higher in the weeks after MMR vaccination than in the weeks beforehand (Table 2). On the contrary, in the third and fourth weeks after vaccination, there were significantly fewer days with health problems than in the corresponding weeks before vaccination. We analysed the same data stratified by time of year to control for the effects of seasons of frequent illness (e.g., spring and autumn). Although the number of days with health problems was greater for children vaccinated in October, November, March and April than for those vaccinated in the rest of the year, the difference in health problems before and after vaccination was identical to the results seen in Table 2.

We examined data on particular symptoms reported by the mothers (Table 3) and found that runny nose was less common after MMR vaccination than before. Fever, on the other hand, was significantly more common in the first week after vaccination than in the week before. However, fever was significantly less frequent by the third week after vaccination than the third week beforehand. Rash was the only symptom consistently more frequent after vaccination. Rashes were twice as frequent in the second week and also significantly more frequent in the third week after vaccination than in the corresponding weeks beforehand.

Three infants were admitted to hospital in the month before vaccination, as compared with the six admitted in the month afterward (three of whom were admitted on or after day 25).

The mean number of physical findings in the physicians' examinations of the children were compared. On average the physicians found 0.5 noteworthy physical findings on the day the MMR vaccine was administered, as compared with 0.91 on day 7 after vaccination (paired $t = 5.68$, $p < 0.001$). Compared with the 7-day findings, 0.75 were noted 30 days after vaccination (paired $t =$

Table 2: Number of days with health problems during the month before and the month after vaccination

Week before and after vaccination*	Mean duration of health problems, d		
	Before vaccination	After vaccination	*p* value†
First (n = 239)	2.2	2.1	NS
Second (n = 241)	2.7	2.5	NS
Third (n = 237)	2.5	2.0	< 0.05
Fourth (n = 192)	2.5	2.0	< 0.05

*The number of mothers who completed the diary for each of the 7 days varied slightly from week to week.
†NS = not significant; paired test was used to determine the *p* values.

2.42, $p < 0.02$). Table 4 shows the proportion of children who had physical findings 7 days after vaccination.

Timing of symptoms

We calculated the proportion of children with symptoms on each of the 15 days after vaccination. Runny nose was most common 5 days after vaccination. Cough occurred in 10.0% to 15.0% of the children from day 4 to day 10 and then decreased in frequency. The time when fever was most likely to occur was approximately 10 days after vaccination, and it was reported in 10.2% of the children. Rash was similar to fever in that 12.0% of the children had a rash around 10 days after vaccination. Runny eyes and swollen glands were not common at any time during the 15 days examined. The daily proportion of children given over-the-counter medications was 14.0% until the 10th and 11th day, when it was 17.1% and 18.1% respectively; it dropped to 10.5% on day 12. In contrast, prescription medicine was given to 5.0% of the children until the 8th day, when the proportion rose to 9.7% and remained there.

Discussion

We found that the morbidity after MMR vaccination did not differ significantly between the 13-month and 15-month groups. It seems that issues of postvaccine morbidity need not enter into the decision of when to give the vaccine.

A strength of this study is that it was conducted in the family practice setting and used observations from three sources; these features permitted a fairly complete picture to be drawn about the childrens' health problems. The mothers' observations in the diaries gave daily information. The physicians' log provided more objective data on physical findings at the seventh day after vaccination such as the status of the child's ear drums and tonsils. Finally, a review of office records and hospital charts provided information on postvaccine conditions serious enough to necessitate medical or hospital care.

The limitations of this study are generalizability and observation bias. The population was limited to rural and urban children in southwestern Ontario, whose parents were educated at a level typical of the region and were compliant with guidelines for vaccinating their children at 1 year of age.

Observation bias may have resulted in the mothers being especially vigilant shortly after vaccination and becoming less so toward the end of the study period. Such bias did not affect the validity of the comparison between the two age groups. However, it may explain differences in morbidity before and after vaccination. We used more than one source of data: although it can be argued that the mothers were subject to observation bias, the same would likely not be true for the physicians' findings, since the reported symptoms and signs (e.g., lymphadenopathy and nasal discharge) have been linked to the MMR vaccine in the product literature. Less vigilant observations by participants who keep diaries has been reported,[14] but not at the 6-week mark, when we noted a decrease in the number of symptoms.

Overcoming observation bias so that the vaccine can be isolated as the cause of the children's illness requires a placebo-controlled trial, which we did not think was ethically justifiable. Such a trial was conducted in Finland[11] and showed some findings similar to ours.

When comparing the mothers' observations with those of the physicians on the same day, we found wide differences. For example, on the seventh day after vaccination runny nose was reported by mothers in approx-

Table 4: Proportion of children with specific physical findings 7 days after vaccination

Finding	No. (and %) of children (n = 240)
Lymphadenopathy	57 (23.8)
Nasal discharge	15 (6.3)
Rash	11 (4.6)
Abnormal tympanic membrane (otitis media)	8 (3.3)
Conjunctival abnormality	8 (3.3)
Abnormal tonsils	2 (0.8)

Table 3: Symptoms reported in the diary for each week before and after vaccination

	Week; % of patients with symptom							
	First		Second		Third		Fourth	
Symptom	Before	After	Before	After	Before	After	Before	After
Cough	19.7	21.8	22.3	24.1	26.0	19.7	27.1	20.7
Fever	7.2	16.8†	17.9	19.2	14.5	7.9*	10.0	9.2
Rash	11.2	13.2	13.8	26.9†	12.4	17.1*	11.3	13.8
Runny eyes	6.0	5.8	9.5	7.3	9.3	5.4	10.9	6.9
Runny nose	29.7	32.9	39.3	37.1	38.0	29.2*	37.6	26.3
Swollen glands	0.1	0.1	0.1	4.9	2.0	1.7	2.4	0.9

*$p < 0.05$, paired *t*-test comparing values before and after.
†$p < 0.01$, paired *t*-test comparing values before and after.

imately 20% of the children, whereas the physicians, viewing the children on that day (and asked specifically to comment on this symptom) recorded it in only 6.3%. This discrepancy has implications for other studies of this type. If physicians and other health care professionals involved in vaccine trials consistently underreport symptoms or if patients overreport, the results of studies that rely solely on one source may be misleading.

A comparison of our findings with those of another Canadian study[8] provides some interesting contrasts. Among the 120 children in that study who received the M–M–R II vaccine the incidence rate of conjunctivitis was 4.2% at day 10, which was similar to our rate of 3.3% at day 7 and is consistent with findings by others.[11] The remainder of the findings in the 1986 report were much higher than our corresponding figures (e.g., tonsillitis 56.7% v. 0.8% respectively, cervical adenopathy 43.3% v. 23.8%). Most surprising, the incidence rate of parotid swelling in the other report was 20.0%; in our study there was not one instance of parotid swelling noted by a physician. Our findings are consistent with other studies of vaccine side effects in this age group.[11] One possible explanation for the high rate of the side-effects in the other study[8] is an unusually high rate of "background" illness at the time of observation. A second possibility is that their diagnostic criteria were different from the conventional ones used by us and the other investigators.

Our finding that prescription drug use increased approximately 7 days after vaccination supports the observation that physicians may be unaware of the common sequelae of MMR vaccination. Although the symptom diaries did not show an increase in symptoms around the seventh day, the physicians' reports on day 7 did show a change from the day of vaccination. These findings presumably account for the reported increased use of prescription drugs. This is perhaps understandable, since the symptoms and signs that were found are not mentioned in the product literature as being vaccine related. As the evidence about the common illness patterns after routine MMR vaccination accumulates, it may be important to include this information in the product literature so that unnecessary treatment is avoided and parents are provided with more accurate information about what to expect in their children.

In conclusion, family physicians should tell parents of children receiving MMR vaccine to watch for fever, cough and runny nose in the first week after vaccination and rash in the second and third week.

Our study was successful in showing that community-based surveillance of adverse reactions to a vaccine can be carried out in family physicians' offices. It can serve as a prototype for further studies of reactions, especially given the increased interest in vaccines and their possible side effects as well as the proliferation of new vaccines expected to be introduced in the near future.

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