Day-to-Day Reactogenicity and the Healthy Vaccinee Effect of Measles-Mumps-Rubella Vaccination

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ABSTRACT. *Objective.* **Revaccination policies adopted in many countries to control measles have raised various safety issues including those concerning the second vaccine dose. We performed a prospective, double-blind, crossover trial among twins receiving a measles-mumps-rubella (MMR) vaccine.**

Study Design. **The study comprised 1162 monozygous and heterozygous twins, each of whom randomly received placebo and then vaccine, or vice versa, 3 weeks apart, at 14 to 83 months of age. Most of the oldest children had previously been vaccinated against measles, and one half of the remainder of children had had the disease. Symptoms and signs were recorded daily on structured forms. Statistical methods included a complex analysis of the vaccine attributability of the symptoms and conditional logistic regression.**

Results. **Vaccination-attributable events occurred in 6% overall. At 14 to 18 months of age, reactions developed between days 6 and 14, peaking at day 10. The clearest vaccine-attributable effect was fever exceeding 101.3 °F (38.5°C; odds ratio: 3.28; 95% confidence interval: 2.23–4.82; $P < .001$), but the same trend was found for rash, arthralgia, conjunctivitis, staying in bed, drowsiness, and irritability. At 6 years of age, systemic reactions occurred 5 to 15 times less frequently, only arthralgia being associated with vaccination. Zygocity, gender, history of allergy, or infections did not modify reactions. Instead, respiratory symptoms developed within days postinjection to a level of 15% to 20% without subsequent decline and with no difference between vaccinees and placebo recipients.**

Conclusion. **Vaccination was avoided during infections, but many small children became mildly ill within a week or so with no relation to vaccination (the healthy vaccinee effect). MMR vaccine was virtually nonreactogenic when given at 6 years of age.** *Pediatrics* **2000;106(5). URL: http://www.pediatrics.org/cgi/content/full/106/5/e62;** ***vaccine, measles, mumps, rubella, reactogenicity, adverse events, zygocity, healthy vaccinee effect.***

ABBREVIATIONS. MMR, measles-mumps-rubella; OR, odds ratio; VA, vaccine attributability.

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The measles components[1–3] used in various measles-mumps-rubella (MMR) vaccines[4,5] have been associated with various short-term and long-term adverse events. This is also true to a lesser extent for the rubella antigen,[6,7] whereas the mumps component (particularly the Jeryl Lynn strain) is deemed virtually harmless.[8] Controlled studies on vaccine reactogenicity are rare,[9] and uncontrolled studies[10–12] exaggerate findings because of a temporal rather than a causal association with vaccination. Very little is known about factors modifying adverse reactions.[13]

We performed a randomized, double-blind, placebo-controlled, and crossover vaccination trial in twins using the MMR vaccine in widest use internationally; the early results were published shortly after the trial.[14] Here we report a thorough analysis of the day-to-day symptoms and signs in 2 age groups with or without previous measles vaccination, and we examine the role of other factors in relation to reactogenicity. We consider such an analysis especially timely because more countries are converting to the use of 2 vaccine doses aimed at eliminating measles and, ultimately, mumps and rubella.

METHODS

Vaccine

Under the auspices of the National Board of Health and the Public Health Institute, a vaccination program to eliminate MMR from Finland was launched in 1982.[15] Over the years, only 1 type of vaccine (MMR_{II}, Merck and Co, Inc, West Point, PA)—consisting of the more attenuated Enders-Edmonston strain of measles virus,[1,4] the Jeryl Lynn strain of mumps virus,[8] and the Wistar 27/3 strain of rubella virus[10]—has been used in the 2-dose schedule. The first dose is administered at 14 to 18 months of age and the second at 6 years of age. Vaccination has been accepted well, with coverage stabilized at ~95%.[16,17] As with all childhood immunizations in Finland, the MMR vaccine is administered on a voluntary basis and free of charge by public health nurses in the ~1000 child health centers of the country.

Twin Study Setup

The trial participants were recruited between November 1, 1982 and October 31, 1983. Public health nurses explained the design to parents of twins attending the child health center and asked for their consent to participate in this prospective study. Detailed instructions had been given earlier to vaccinators at a series of seminars organized throughout the country.

Parents of 581 twin pairs (1162 children) 14 months through 6 years of age consented to and completed the study. In each pair, 1 child was randomly allocated a green and the other an orange color code, with all materials color-marked accordingly. Each twin pair's vaccination pack contained 2 doses of vaccine and 2 of placebo. Hence, each child received 1 dose of vaccine followed by 1 of placebo—or vice versa—3 weeks apart. Nurses, parents, and investigators were all blind to the order of injection.

Data Collection

Because all short-term reactions were expected to occur within 3 weeks postvaccination,[9–12] parents were given a specially designed questionnaire for each child to be filled in daily for 21 days after both injections. The following items were monitored: local reactions (redness with a diameter exceeding 1 inch, soreness, swelling), rectal temperature (mild fever: <101.5°F/38.6°C; moderate fever: between 101.5°F/38.6°C and 103.1°F/39.5°C; high fever: further elevated), rhinorrhea or cough, nausea or vomiting, diarrhea, rash, arthralgia, conjunctivitis, staying in bed, drowsiness, irritability, and other potential symptoms. Free rectal thermometers were distributed for uniform measurement of body temperature.

The nurses had their own questionnaire. They interviewed the parents for history of allergy, number of respiratory infections during the past 12 months, any history of a recent contact with or passed disease of MMR, and earlier vaccination against measles. The information on zygosity was obtained from hospitals. Twins were deemed homozygous unless of different gender or unless they had had clearly separate placentas or microscopically distinct fetal membranes.

Statistical Methods

Statistical analyses were performed, unless otherwise indicated, using SAS statistical software standard procedures (SAS, Cary, NC).[18] Conditional logistic regression models were used to study modifying factors.[19]

The timing of symptoms and signs in relation to injections was recorded to create analyzed daily profiles. The results confirmed that postvaccination days 6 to 14 formed the primary risk period.[4,9–12] Hence, symptoms and signs appearing during these 9 days were regarded as potentially caused by MMR vaccine. In the dichotomous analysis, a symptom or sign was taken as positive for the injection if it was present during any day of the risk period.

The simple rate difference of each symptom and sign was analyzed with McNemar's test for paired data. A conditional logistic regression model was used to estimate the effects of various factors and was expressed as the adjusted odds ratio (OR) for each postvaccination symptom in the matched data.[19] A summary variable, any MMR-related event, comprising all symptoms and signs except mild fever (≤101.3°F/38.5°C) and those affecting the respiratory or gastrointestinal tracts—which have innumerable causes other than vaccination—was deduced from the aforementioned analysis.

The number of days that each individual symptom or sign was present during the 9-day period postinjection was calculated separately for each twin. From these results we calculated the vaccine attributability (VA) score with this formula:

$$\text{VA score} = [(\text{Vac}_{VP} - \text{Pla}_{VP}) + (\text{Vac}_{PV} - \text{Pla}_{PV})]:2,$$

in which Vac and Pla indicate the number of days with the symptom or sign present during days 6 to 14 postinjection, while V for vaccine and P for placebo show the order in which the injections had been administered. Thus, the VA score expresses the mean increase (or decrease, if negative) in days of the presence of a particular symptom or sign in a pair of twins postvaccination and postplacebo.

We then calculated a summary score, systemic MMR-related event, as the sum of the VA scores of the same variables as in any MMR-related event. This score was the most sensitive indicator of the VA events overall (Table 1), and it was used in the analysis of age, allergy, previous measles, mumps or rubella, or previous measles vaccination. The effects of these potential confounders in vaccinees versus placebo recipients were tested with the standard t test.

Only 6 (3/230 pairs; 1.3%) of the 1-year-olds (n = 460) had previously been vaccinated against measles, whereas the great majority (313/351 pairs; 89%) of those 2 years of age or more (n = 702) had been vaccinated. Of the 76 older children not previously vaccinated against measles, 42 (55%) had experienced natural measles.

Effect of Gender and Zygocity

The possible effects of gender and zygocity were analyzed with this formula:

$$\text{symptom score difference} = |(\text{Vac}_{VP} - \text{Pla}_{VP}) - (\text{Vac}_{PV} - \text{Pla}_{PV})|,$$

in which the abbreviations are the same as in the VA score. Because gender turned out not to influence reactogenicity, the genetic disposition could be analyzed by comparing the twin pairs of the different genders (certainly heterozygotic) with the homozygotic twins.

RESULTS

Reactions After the First and Second Injections

For all symptoms and signs checked—although especially for rash, irritability, and conjuctivitis—the difference between vaccinees and placebo recipients was slightly greater in the subset of twins who received vaccine before placebo. This was doubtless because of diminished motivation to report every single detail after the second injection. However, conditional logistic regression analysis did not show significant effect of the order of injections.

Local reactions occurred during the first 2 postinjection days in 4% of participants, regardless of whether vaccine or placebo was given; Fig 1 shows this for all 1162 twins combined. Redness was more common than was edema. Sensation of stinging was not specifically mentioned.

TABLE 1. VA Score in the Two Study Groups*

Symptoms	14 to 18 Months of Age			>6 Years of Age		
	Mean (Days)	SD	P Value	Mean (Days)	SD	P Value
Fever >103.1°F (39.5°C)	.08	.37	.001	.00	.11	>.10
Fever >101.3°F (38.5°C)	.34	.87	<.0001	.01	.30	>.10
Fever >99.5°F (37.5°C)	.51	1.20	<.0001	.04	.60	>.10
Respiratory symptoms	−.06	1.53	>.10	−.06	1.33	>.10
Nausea and vomiting	−.00	.30	>.10	−.03	.34	>.10
Diarrhea	.06	.54	>.10	.01	.24	>.10
Rash	.17	1.39	.07	−.00	.66	>.10
Arthralgia	.06	.48	.07	.05	.37	.007
Conjunctivitis	.19	.84	.0008	.03	.40	>.10
Staying in bed	.17	.61	.0008	.02	.33	>.10
Tremor	.03	.27	.09	.00	.05	>.10
Drowsiness	.21	.84	.002	.03	.47	>.10
Irritability	.49	1.72	.0001	−.03	.69	>.10
Systemic MMR-related events	1.67	4.49	<.0001	.11	1.72	>.10

SD indicates standard deviation.
* The difference from zero was tested by t test.

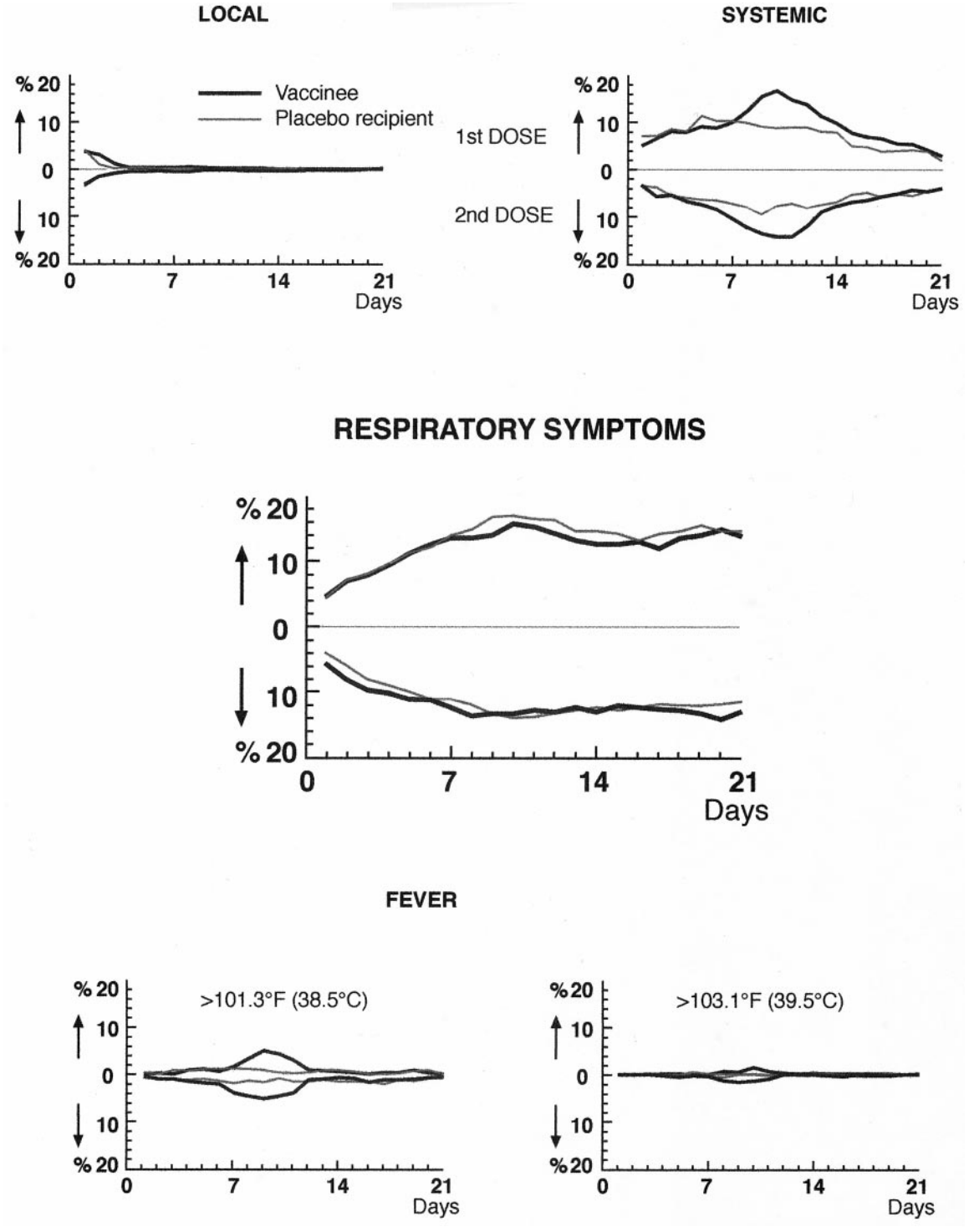

Fig 1. Day-to-day occurrence of systemic, local, and respiratory symptoms and signs, and fever in vaccinees (thick red line) and placebo recipients (thin green line). The upper lines depict the first injections, the lower (with inverted scale) the second injections. Systemic refers to systemic MMR-related events, which includes fever exceeding 101.3°F (38.5°C), rash, arthralgia, conjuctivitis, staying in bed, drowsiness, and irritability.

Systemic MMR-related events, ie, any symptom or sign (or combination) except those affecting the respiratory or gastrointestinal tracts during days 6 to 14 postvaccination, peaked on day 10 after both the first and the second injection, regardless of their order. Overall, 6% of vaccinees had events attributable to MMR vaccination.

Respiratory symptoms and signs behaved in an entirely different manner (Fig 1). Their frequency increased by 15% to 20% during the first 10 days postinjection and did not subsequently decline. Surprisingly, this occurred identically in vaccinees and placebo recipients.

Fever was the most common systemic sign observed (Fig 1). Moderate or high VA elevation of temperature occurred in 4% (12% of vaccinees vs 8%

of placebo recipients). For moderate fever, the preponderance of vaccinees was rather clear (Fig 1) because it developed in 25% and 6% of 14- to 18-month-old vaccinees and placebo recipients, respectively, the difference being highly significant (Tables 1 and 2). Only 3% of both groups of 6-year-olds developed moderate or high fever. High fever was rare on a day-to-day basis (Fig 1), but at 14 to 18 months it occurred in 7% of vaccinees and 3% of placebo recipients—a significant difference (Tables 1 and 2). Among the 6-year-olds, just .5% of children in both groups experienced high fever.

Figure 2 shows the behavior of 9 individual symptoms and signs in all twins combined. Slightly more reactions were observed among vaccinees than among placebo recipients for all symptoms and signs investigated except nausea or vomiting and diarrhea. Table 1 indicates the dramatically lower frequency of symptoms and signs in the older vaccinees.

Control of potential confounding by injection order and presence of other selected symptoms did not change the order or relative impact of the vaccine-related symptoms and signs in the 14- to 18-month-olds (Table 2) or in the 6-year-olds.

Effect of Previous Measles Vaccination and Age

One percent of the 14- to 18-month-olds and 89% of the 6-year-olds had received measles vaccination before MMR. Without regard to previous measles immunization, the sum of the VA scores for probable MMR reactions was 1.67 in the younger versus .11 in the older group—a 15-fold difference (Table 1). The previously vaccinated children experienced 16 times less symptoms and signs than did nonvaccinees, the sums of the VA scores being .09 versus 1.46, respectively (Table 3).

Whether this major difference in reactogenicity was attributable to immunologic reasons (previous measles, vaccination, or measles contact), to age only, or to both factors could not be assessed, although immunology seems more likely. In the older subjects, of the 38 twin pairs not vaccinated against measles before, 21 pairs had undergone natural measles. The fivefold higher sum of the VA scores in the previously nonvaccinated versus vaccinated children was, therefore, not significant. In contrast, a similar difference between groups in moderate and high fever was significant ($P = .02$ and $P = .03$, respectively, Table 3).

Arthralgia was the only symptom among the 6-year-olds that was associated with vaccination (Table 1). Previous mumps, rubella, or known atopy was not associated with reactogenicity.

TABLE 2. Adjusted OR From Conditional Logistic Regression Analysis for the MMR Vaccine-Related Symptoms and Signs Among the 14- to 18-Month-Old Twins

Symptom or Sign	OR	95% CI	*P* Value
Fever ≥103.1°F (≥39.5°C)*	2.83	1.47–5.45	.002
Fever ≥101.3°F (≥38.5°C)†	3.28	2.23–4.82	<.001
Fever ≥99.5°F (≥37.5°C)*	2.66	1.66–3.08	<.001
Respiratory symptoms‡	2.66	1.66–3.08	<.05
Nausea or vomiting§	.70	.44–1.10	>.05
Diarrhea‡	1.18	.75–1.87	>.05
Exanthema	1.77	1.27–2.47	<.001
Arthralgia‖	3.66	1.74–7.70	<.001
Conjunctivitis‡	2.49	1.59–3.90	<.001
Staying in bed*	1.83	1.10–3.03	.02
Drowsiness	Model not fitted		
Irritability*	1.60	1.19–2.16	.002
Any MMR-related event*	1.62	1.30–2.03	<.001

CI indicates confidence interval.
The ratios were adjusted for the effects of the injection order and the following events: * gastroenteritis, nausea or vomiting, and respiratory symptoms; † gastroenteritis, nausea or vomiting, respiratory symptoms, and allergy; ‡ nausea or vomiting; § diarrhea; and ‖ respiratory symptoms.

Effect of Zygocity

Forty-one percent of the 487 heterozygotic pairs (202) were of different gender and, thus, certainly heterozygotic. The symptom score difference for any fever was higher among heterozygotics (1.51 vs .85; $P = .04$), but for other variables there were no differences between homozygotics and heterozygotics.

DISCUSSION

This study is a response to the need for an adequately controlled study assessing adverse events in relation to MMR that would otherwise not have come to medical attention.[13] The short-term reactions in causal association with MMR vaccination proved dramatically less common than was suggested by 3 previous uncontrolled studies.[10–12] Most symptoms and signs commenced 5 to 7 days postvaccination and peaked on day 10 (Figs 1 and 2), suggesting that they were primarily caused by the measles component—the usual incubation period of measles is 8 to 12 days versus 16 to 18 days for rubella and mumps.[20]

Local reactions (in ~4%; Fig 1) were attributable to mechanical trauma, because there was no difference between vaccinees and placebo recipients. Regarding systemic reactions, fever was the sign most uniformly caused by MMR vaccination (Table 2; Figs 1 and 2), although conditional logistic regression analysis showed the same trend for rash, arthralgia, conjunctivitis, staying in bed, drowsiness, and irritability. In contrast, respiratory symptoms and signs (and diarrhea, nausea, and vomiting; Figs 1 and 2) were clearly not attributable to MMR vaccination but to other concurrent factors,[21,22] probably commonplace infections. The presence of these symptoms also understandably increased the probability of fever, arthralgia, conjunctivitis, staying in bed, and irritability.

Most interesting was the steady increase in respiratory symptoms and signs for 7 to 9 days postinjection in vaccinees, and, surprisingly, in placebo recipients too, without a subsequent decline from the 15% to 20% level reached (Fig 1). Because vaccinations were given in a relatively symptom-free state, both populations only returned to the usual frequency of trivial symptoms and signs within a week or so postinjection (Fig 1). This healthy vaccinee effect[13,21] has never been so indisputably documented before. Were this phenomenon fully understood—and explained to parents before vaccination—many misunderstandings (and lawsuits) would be avoided.

Our data also add much to knowledge about the

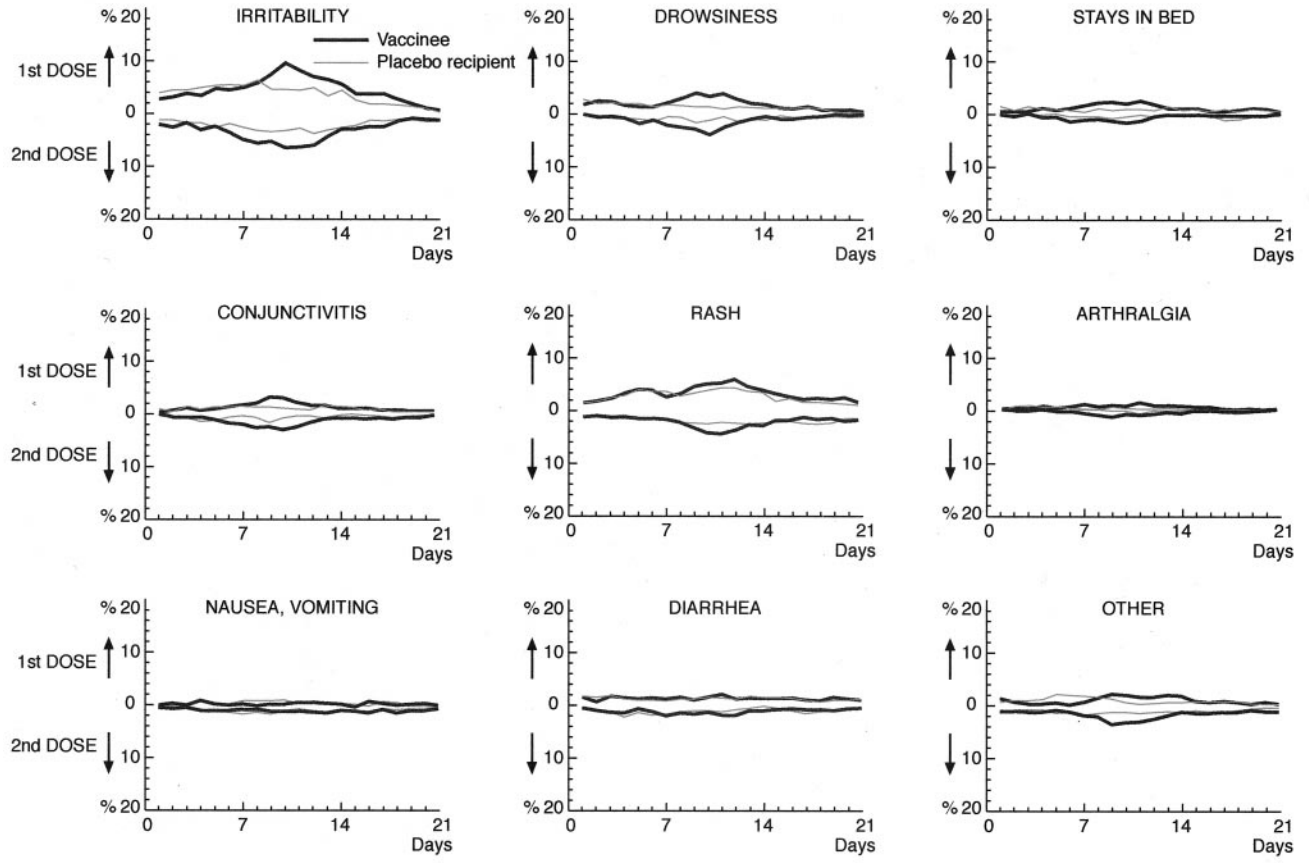

Fig 2. Day-to-day occurrence of other symptoms and signs in vaccinees (thick red line) and placebo recipients (thin green line). The upper lines depict the first injections; the lower (with inverted scale), the second injections.

TABLE 3. VA Score for Symptoms and Signs in Relation to Previous Measles Vaccination

	Age	Not Vaccinated			Vaccinated		*P* Value	
		Mean (Days)	SD	*n**	Mean (Days)	SD		*n**
All MMR-related events	All	1.46	4.26	263	.09	1.70	316	.0001
	6 y	.39	1.86	38	.08	1.70	313	>.10
Fever ≥101.3°F (≥38.5°C)	6 y	.16	.44	38	−.01	.28	313	.02
Fever ≥99.5°F (≥37.5°C)	6 y	.26	.63	38	.01	.59	313	.03

SD indicates standard deviation.
* Twin pairs.

effects of the second dose of MMR vaccine. When aiming to eliminate measles, as well as mumps and rubella, the reactogenicity of the second dose is a critical issue, much more so than for the first dose, about which there is no choice—the child must be immunized anyway, unless he or she is to be intentionally left at great risk of these diseases and their various complications.

Because this was not a cohort study, we could not define the effects of the second dose of MMR vaccine in the same child. Despite this limitation, it was evident that the vaccine was virtually nonreactogenic at 6 years of age (Table 1). Because >95% of the 6-year-olds had already either received measles vaccination or experienced the disease, the age effect as such could not be delineated. However, the slightly higher VA scores for moderate and high fever and the nonsignificant increase in the sum of the VA scores for all MMR-related events in placebo recipients (Table 3) suggest that low reactogenicity in the older children was attributable primarily to measles immunity. We deem the second MMR vaccination to be virtually harmless, at least when the interval between doses does not exceed 5 years.

A retrospective survey in the United States[13] showed that a second dose of MMR vaccine was more reactogenic when given at 11 to 12 years of age (former recommendation of the American Academy of Pediatrics, Red Book Committee, which now has changed the recommendation to the age of 4 to 6 years[20]) than at 4 to 5 years (as advised by the Advisory Committee on Immunization Practices).[23] Administration of the second dose a decade after the first dose (as occurred often in the United States[13] and Sweden[24]) may increase the risk of reactions because such a long interval in circumstances with

no or very few contacts with natural measles might have increased the risk of waning immunity.[25,26]

Secondary failures of MMR vaccination have been calculated to occur as rarely as in .2% (or less) of vaccinations,[27] but this information is derived from populations occasionally boosted by natural measles.[28] Our experience in Finland is that the documented interruption in the circulation of MMR viruses[29,30] has led to much higher figures for secondary vaccine failures.[31,32] We predict that waning immunity will be a growing problem in countries at or close to the elimination of MMR. The virtual nonreactogenicity of the second dose of MMR vaccine in previously immunized children should encourage other countries to proceed to the 2-dose regimen. Only then might the elimination of these diseases be realized.

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