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ARTICLE

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ABSTRACT

BACKGROUND/OBJECTIVES. In 1989, the American Academy of Pediatrics and the Advisory Committee on Immunization Practices recommended that school children receive 2 doses of measles-mumps-rubella vaccine. With measles and rubella eliminated from the United States, measles-mumps-rubella vaccine adverse events have come under scrutiny, but no study has compared the reactogenicity of the first (measles-mumps-rubella vaccine dose 1) and second (measles-mumps-rubella vaccine dose 2) doses at the most common ages of administration in the United States.

METHODS. From a health maintenance organization, 3 groups of children were recruited: (1) toddlers aged 12 to 24 months receiving measles-mumps-rubella vaccine dose 1; (2) kindergartners aged 4 to 6 years receiving measles-mumps-rubella vaccine dose 2; and (3) middle schoolers aged 10 to 12 years receiving measles-mumps-rubella vaccine dose 2. From 2 weeks before measles-mumps-rubella vaccine administration until 4 weeks afterward, families recorded in diaries the occurrence of potentially common symptoms. Postvaccination symptom rates were compared with the prevaccination baseline, with significance assessed by testing incidence rate ratios estimated by Poisson regression.

RESULTS. Of 2173 children enrolled, 373 (17%) were lost to attrition, producing a study population of 1800. Compared with the prevaccination baseline, rates of fever, diarrhea, and rash were significantly elevated postvaccination among 535 toddlers receiving measles-mumps-rubella vaccine dose 1. An estimated net 95 (18%) experienced measles-mumps-rubella vaccine-associated events (median onset 5–10 days postvaccination, duration 2–5 days), with high fever (temperature ≥39.5°C) occurring in 33 (6%). None required medical attention. For 633 kindergartners and 632 middle schoolers, symptom rates were not significantly elevated after measles-mumps-rubella vaccine dose 2 compared with baseline.

CONCLUSIONS. Vaccination-associated adverse events occur in ~1 of every 6 toddlers receiving measles-mumps-rubella vaccine dose 1, with high fever occurring in 1 of 20. Adverse events are infrequent for measles-mumps-rubella vaccine dose 2 administered to school-aged children.

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The findings and conclusions expressed are those of the authors and do not necessarily represent the views of CDC.

Key Words
measles, mumps, and rubella vaccine, adverse reactions, second dose, dose schedule

Abbreviations
ACIP—Advisory Committee on Immunization Practices
AAP—American Academy of Pediatrics
MMR—measles-mumps-rubella vaccine
CDC—Centers for Disease Control and Prevention
MMR1—first dose of measles-mumps-rubella vaccine
MMR2—second dose of measles-mumps-rubella vaccine

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In 1989, facing a nationwide measles epidemic among vaccinated school children, the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommended that school-aged children receive a second dose of measles-mumps-rubella vaccine (MMR) to provide disease protection among those in whom the first dose had failed to induce immunity.[1,2] Implementation was swift. In 1988, the year before the recommendation, ~6 million MMR doses had been administered nationally. In 1990, the year after the recommendation, this rose to >16 million doses. Since then, the number has never fallen below 12 million annually, enough vaccine to provide 2 doses to each child in a US birth cohort of 4 million, plus catch-up doses to 4 million others (Centers for Disease Control and Prevention [CDC] unpublished data, 2006). The disease impact was dramatic. The number of school-aged children with measles fell from 7351 in 1989 to 72 in 1995, and ≤70 cases have been reported annually since 2000 (CDC unpublished data, 2006). Ongoing measles virus transmission was declared eliminated from the United States in 2000,[3] followed by rubella in 2004.[4]

In the early 1990s, based on then-divergent ACIP and AAP recommendations,[1,2] some states passed laws requiring the second dose of MMR (MMR2) for kindergarten entry (27 states by 1994), others for middle or junior high school entry (12 states by 1994). In 1998, ACIP and AAP agreed on a kindergarten recommendation,[5,6] but it was not until 2005 that all states began to enforce a kindergarten requirement. Diversity in recommended ages for MMR2 is seen among different nations in Europe.[7] In developing countries, second doses of measles vaccine are often administered as part of mass campaigns that target a wide age range from infancy through teenaged years.[8] The optimal age for a second dose, based on immunogenicity or reactogenicity, has not been well defined.

In the absence of measles disease in the United States, public and media attention has increasingly focused on vaccine-adverse events, raising concern that vaccine uptake might be reduced to the point where endemic measles transmission could return.[9,10] However, few studies have examined adverse events of measles-containing vaccine beyond the first dose.[11–15] Although a number of studies have attempted to evaluate rare and delayed adverse events putatively associated with MMR (eg, autism and epilepsy),[16,17] none has compared common and immediate adverse events associated with administration of the first and second doses of MMR at the ages at which these doses have usually been administered in the United States. We report the results of such a study.

METHODS

Primary Objective

The primary purpose of this work was to evaluate rates and patterns of potentially common adverse events occurring within a month after receipt of the first and second doses of MMR vaccine, when administered to healthy children at the commonly recommended ages for school entry in the United States in a setting where wild disease exposure and boosting were unlikely to have occurred before vaccination.

Secondary Objectives

The secondary purposes of this work were to compare adverse event rates for: (1) the first (MMR1) and second (MMR2) doses of vaccine and (2) MMR2 at the 2 ages when it has been most commonly administered: 4 to 6 years (kindergarten) versus 10 to 12 years (middle school).

Setting

The study population was drawn from patients of Marshfield Clinic, a comprehensive health maintenance organization that is the principal health care provider for a rural area of central Wisconsin. The clinic has a longitudinally stable patient population with a low rate of use of services outside the clinic. The clinic maintains a central vaccination registry, captures other health events by computer, and is 1 of 8 health maintenance organizations participating in the Vaccine Safety Datalink project.[18] The state of Wisconsin had enacted a law in 1991 requiring documentation of MMR2 receipt for kindergarten and grade 6 entry. The 7 counties surrounding the clinic, with a total population in 2000 of 364 187,[19] reported 41 confirmed cases of measles during 1985–1994 and no cases thereafter through 2005 (CDC unpublished data, 2006).

Study Groups and Enrollment

Three age groups of children were enrolled prospectively over a 2-year period: group 1, 12 to 24 months old scheduled to receive MMR1 ("toddlers-MMR1"); group 2, 4 to 6 years old scheduled to receive MMR2 to meet the kindergarten entry requirement ("kindergarteners-MMR2"); and group 3, 10 to 12 years old scheduled to receive MMR2 to meet the middle school entry requirement ("middle schoolers-MMR2"). Vaccine was administered by study nurses in standard protocol in accord with school vaccination requirements. No child entering kindergarten had vaccine deferred until middle school entry. Candidate study subjects were excluded if they had: (1) previously had measles, mumps, or rubella disease; (2) lived in the same household with anyone who had had these diseases during the subject's lifetime; (3) previously received any component of MMR vaccine other than as specified; (4) received any other vaccinations within 30 days of study start; (5) had any contraindication to MMR vaccination as specified in the recommendations of the ACIP; or (6) had any condition likely to impair immune response to MMR vaccine, as specified in ACIP recommendations.[5] In addition, chil-

dren scheduled to receive MMR2 were excluded if they had not received MMR1 previously between the ages of 12 and 24 months. Parents of study subjects were provided with informed permission materials, and middle school children were additionally provided with informed assent materials. The study was approved by the human subjects protection offices of both the Marshfield Clinic and CDC.

Study Design and Data Acquisition

Because study vaccinations were required by law for school attendance, it was not considered possible or ethical to recruit a separate control group from whom vaccines were withheld. Instead, within the study population, a designated period preceding vaccination was treated as a baseline for rates of specified health events to which rates in the postvaccination period were compared. Specifically, 2 weeks before vaccination, the family of each participant was prospectively provided with a prevaccination diary on which to record daily by check mark the occurrence of 13 symptoms identified in the literature as potentially associated with MMR vaccination: fever, runny nose, sore throat, cough, red eyes, nausea, vomiting, diarrhea, jaw swelling, swollen glands, joint problems, headache, and rash. A space was provided for recording other symptoms. If no symptoms were present, the family was instructed to check "none." If fever was suspected, the family was instructed to take a temperature with a supplied thermometer (rectally for the toddlers and orally for the older children), to record the temperature, and to continue doing so at least daily until the child became afebrile. Because most children aged 12 to 24 months were deemed unable to provide meaningful information about headache, nausea, and sore throat, these symptoms were omitted for group 1 (toddler-MMR1). The prevaccination diary, on completion, was brought to the clinic, where it was reviewed by the study nurse. Vaccine was administered, and the family was provided with an identically structured 4-week postvaccination diary. The postvaccination diary, on completion, was mailed to the study nurse, who reviewed it, with telephone consultation with the family as needed. The study nurse was available to families for assistance with diary completion or discussion of health events at any time during the 6-week observation period. Any visits to the clinic or health interactions with the clinic personnel were captured by the system of computerized medical charts. Other data recorded about study subjects included date of birth, documented dates of all vaccinations, gender, and parent-declared race/ethnicity. Children were enrolled throughout the calendar year as they became age eligible for vaccination, although a mode occurred in August before school entry. No unusual levels of community illness were encountered during the study period.

Statistical Analysis

Diary data were analyzed using SAS 9.1 (SAS Institute, Cary, NC). Fever was considered present if the recorded temperature was ≥38.0°C (100.4°F).[20,21] For bivariate comparisons between groups, the χ^2 test was used for categorical variables and the Wilcoxon rank sum test for continuous variables. For each of the 4 postvaccination weeks (week +1 through +4), rates of children with each symptom were compared with a prevaccination baseline week (week −2). Significance was evaluated by testing incidence rate ratios, estimated by Poisson regression with generalized estimating equations, to account for correlation of repeated measures and controlling for other vaccinations administered simultaneously. A symptom was deemed potentially vaccine associated if its rate in a postvaccination week was significantly elevated over the prevaccination baseline. To estimate the net excess rate for such symptoms, the prevaccination baseline rate was subtracted from the postvaccination rate. Symptom characteristics of vaccine-associated adverse events were examined: day of onset after vaccine administration, duration of symptom, and fever intensity. Secondary analyses were performed by: (1) removing other vaccinations from the model and (2) including gender in the model. The potential influence of seasonality, particularly for respiratory illness, was examined by comparing the net symptom rates for different periods of the year. Depending on the baseline rate of symptoms, a twofold increase in postvaccination rates over baseline could be detected by a sample size of 600 subjects in each group, or 1800 subjects total. Anticipating a 15% to 20% attrition rate, the initial study population target was 2200 subjects.

RESULTS

Study Population

A total of 2173 children were enrolled, of whom 373 (17%) were lost to attrition over the 6-week observation period, producing a final study population of 1800 (Fig 1). Failure to complete the prevaccination diary accounted for 66% (245 of 373) of subject loss and was most frequent among group 1 (toddlers-MMR1), who had the highest overall attrition rate (23%), compared with 14% and 15% for the other groups ($P < .001$). Reflecting the rural Midwestern source population, 99% (1776 of 1800) of the overall study population was non-Hispanic white, with no significant racial/ethnic differences among groups (Table 1). However, the 2 younger groups were significantly ($P < .001$) more likely than the older group to receive other vaccinations at the same time as MMR: 89% of group 1 (toddlers-MMR1) and 81% of group 2 (kindergarteners-MMR2) vs <1% of group 3 (middle schoolers-MMR2). For the 535 toddlers, vaccines containing Haemophilus influenzae type b were most frequently coadministered (440 [82%]),

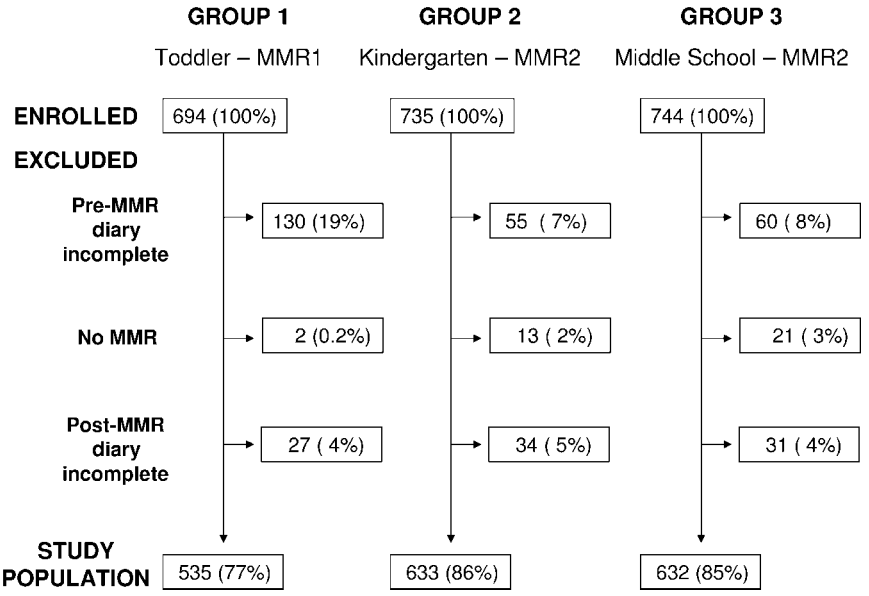

FIGURE 1
Study population enrollment, exclusions, and retention.

TABLE 1 **Study Population Characteristics, MMR1 and MMR2 Adverse Events Study**

Group	*N*	Age at MMR, Median (Range)	Gender Female, *n* (%)	Race/Ethnicity Non-Hispanic White, *n* (%)	Other Immunizations	
					Any, *n* (%)	Pertussis-Containing, *n* (%)
1 toddler-MMR1	535	15.1 (12.0–19.7) mo	245 (46)	525 (98)	476 (89)	233 (44)
2 kindergarten-MMR2	633	5.2 (4.1–6.7) y	308 (49)	623 (98)	511 (81)	485 (77)
3 middle school-MMR2	632	11.3 (10.0–12.9) y	303 (48)	628 (99)	5 (1)	1 (0.2)

followed by pertussis (233 [44%]) and polio (95 [18%]). For the 633 kindergartners, the relative frequency was polio (495 [78%]), pertussis (485 [77%]), and others (31 [5%]). Varicella vaccine was not administered to any study subject.

Symptom Rates

Among the 13 symptoms examined, 3 were found to be significantly increased in the postvaccination period compared with the prevaccination baseline, 6 were not found to be significantly changed, and 4 were found to be significantly decreased. The findings were not changed when simultaneous administration of other vaccines or gender was included in the model. During the 6-week observation period, no study subject was known to have had any health event requiring medically attended treatment.

Significantly Increased

Among toddlers receiving MMR1 (group 1), fever, diarrhea, and rash were reported significantly more frequently in each of the 2 weeks immediately after vaccination than in the prevaccination control period (Fig 2). The proportion of children with ≥1 of these symptoms was 21% (112 of 535) at baseline and rose to 52% (278 of 535) for the 2-week period after vaccination. In contrast, relatively few (<6%) of the older children receiving MMR2 (groups 2 and 3) reported any of these symptoms at baseline, and no significant change in rates occurred postvaccination.

No Significant Change

Baseline and peak rates of conjunctivitis, nausea, vomiting, lymphadenopathy, joint pain, and swollen jaws were relatively low for all groups (<6%; Fig 3). Postvaccination increases were observed for some symptoms among some groups, but numbers were small and did not attain statistical significance.

Significantly Decreased

Baseline rates of coryza, cough, pharyngitis, and headache were high (eg, 40% of toddlers had runny noses) and tended to show small, slow, steady declines over the observation period, attaining statistical significance by the third or fourth week postvaccination (Fig 4). These patterns did not change when children vaccinated April through September were compared with those vaccinated October through March.

Vaccine-Associated Adverse Events

Analysis was restricted to the 52% (278 of 535) of toddlers in group 1 who had fever, diarrhea, or rash during the 2 post-MMR1 weeks when these symptoms were significantly elevated over baseline.

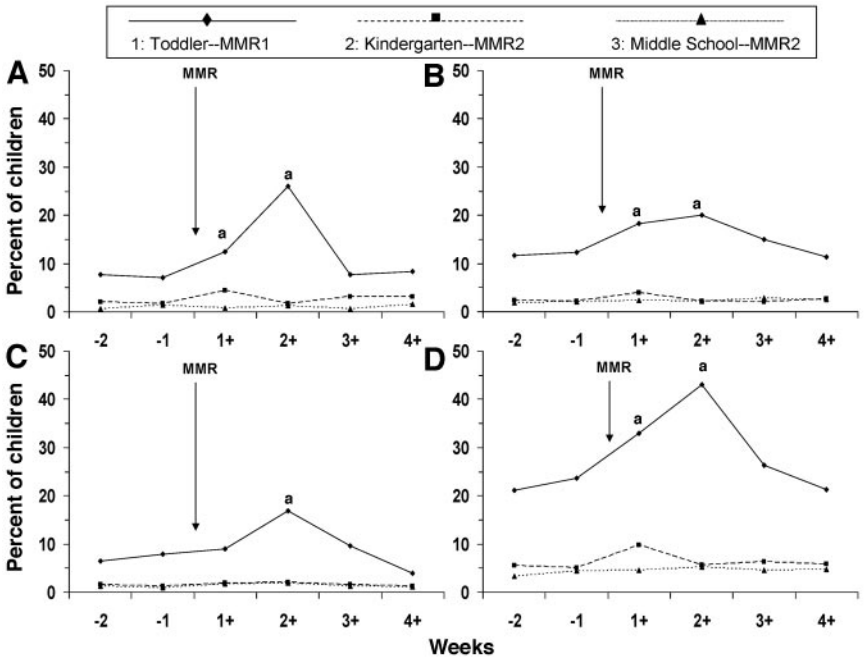

FIGURE 2
Postvaccination symptom rates significantly elevated over baseline. X-axis shows weeks relative to date of vaccination. Y-axis shows percentage of children in each group with symptom. A, fever; B, diarrhea; C, rash; D, fever, diarrhea, or rash. Groups are plotted separately: group 1 (toddlers receiving MMR1, $N = 535$) —; group 2 (kindergartners receiving MMR2, $N = 633$) ----, group 3 (middle schoolers receiving MMR2, $N = 632$) . . . . [a] Postvaccination weeks in which symptom rates were significantly elevated over prevaccination baseline.

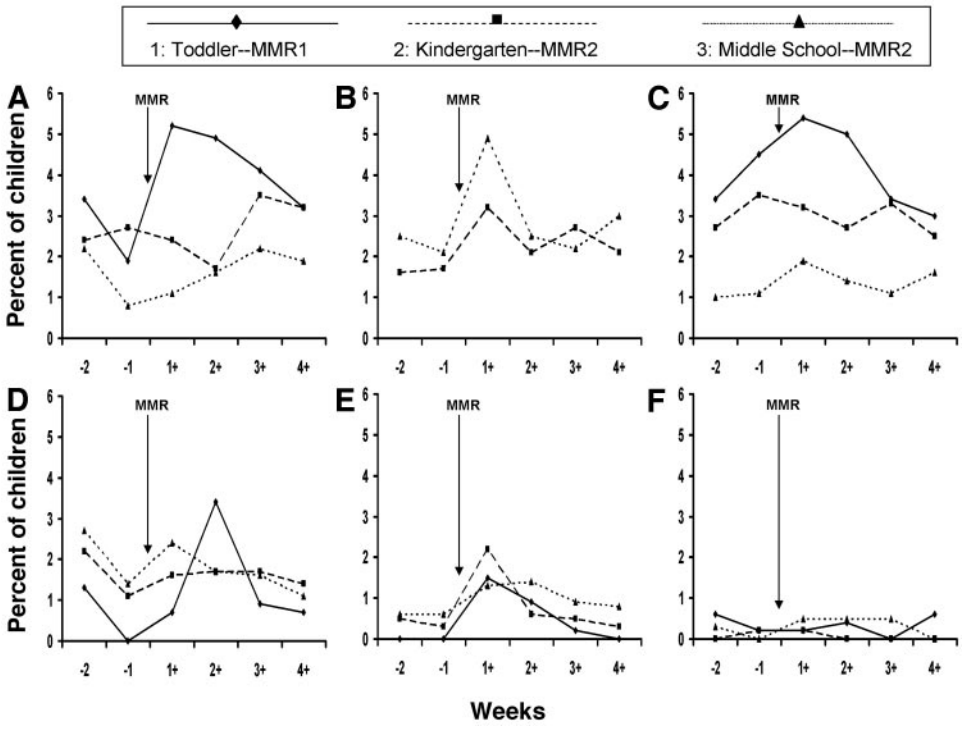

FIGURE 3
Postvaccination symptom rates with no significant change from baseline. X-axis shows weeks relative to date of vaccination. Y-axis shows percentage of children in each group with symptom. A, conjunctivitis; B, nausea; C, vomiting; D, lymphadenopathy; E, joint pain; F, swollen jaw. Groups are plotted separately: group 1 (Toddlers receiving MMR1, $N = 535$) —, group 2 (kindergartners receiving MMR2, $N = 633$) ----, group 3 (middle schoolers receiving MMR2, $N = 632$) . . . . Data about nausea was not captured for group 1 toddlers.

Event Rates

When baseline prevaccination symptom rates were subtracted from the postvaccination rates, the net excess rates were much lower than crude rates: of the 278 children with fever, diarrhea, or rash in the 2 weeks post-MMR1, an estimated 95 (34%) had symptoms associated with vaccination (Table 2).

Symptom Patterns

During the baseline period, 80% (90 of 113) of toddlers had fever, diarrhea, or rash singly, whereas 78% (74 of 95) of toddlers with vaccine-associated symptoms had grouped symptoms ($P < .001$): fever and diarrhea, 32%; fever and rash, 25%; fever, diarrhea, and rash, 21%; fever alone, 18%; and rash alone, 4%. Almost all of the

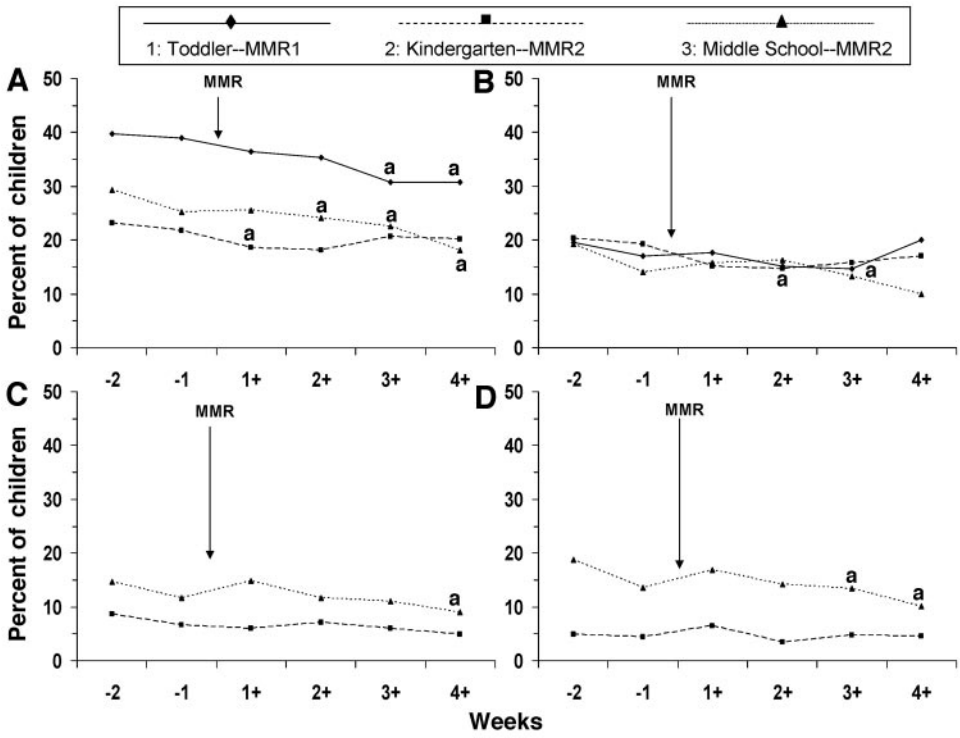

FIGURE 4
Postvaccination symptom rates significantly decreased from baseline. X-axis shows weeks relative to date of vaccination. Y-axis shows percentage of children in each group with symptom. A, coryza; B, cough; C, pharyngitis; D, headache. Groups are plotted separately: group 1 (toddlers receiving MMR1, $N = 535$) —, group 2 (kindergartners receiving MMR2, $N = 633$) ----, group 3 (middle schoolers receiving MMR2, $N = 632$) . . . . [a] Postvaccination weeks in which symptom rates were significantly decreased compared with the prevaccination baseline. Data about pharyngitis and headache were not captured for group 1 toddlers.

TABLE 2 **Symptoms Significantly Elevated During Postvaccination Period Compared With Prevaccination Baseline Among Children Aged 12 to 20 Months Who Received MMR1 ($N = 535$ children)**

Symptom	Baseline Period (Week −2)		Postvaccination Period (Week +1 and +2)			
	Children	%	Crude[a]		Estimated Net[b]	
			Children	%	Children	% (95% Confidence Interval)
Fever	41	7.7	173	32.3	91	17.0 (10.9–23.1)
Diarrhea	62	11.6	153	28.6	50	9.3 (2.9–15.8)
Rash	34	6.4	90	16.8	48	9.0 (4.6–13.4)
Fever, diarrhea, or rash	113	21.1	278	52.0	95	17.7 (9.4–26.1)

Weeks are numbered relative to date of MMR1 vaccination.
[a] "Crude" indicates the total number and percentage of children reported to have symptom during postvaccine weeks when symptom rate was significantly elevated over baseline.
[b] "Estimated Net" indicates the net number and percentage of children with postvaccination symptoms in excess of baseline rate. A daily net incidence rate was obtained by subtracting the daily incidence rate for the baseline period from the daily incidence rate for the postvaccine weeks when the symptom was significantly elevated. The net number of children with a vaccine-attributable symptom was estimated by multiplying the daily net incidence rate by the number of postvaccination days that the symptom was significantly elevated.

toddlers (91 of 95 [96%]) with vaccine-associated symptoms had fever, compared with approximately one third (41 of 113 [36%]) of toddlers with fever, rash, or diarrhea during the baseline period ($P < .001$).

Onset, Duration, and Fever Intensity

Onset of all 3 of the symptoms was bimodal, with an initial peak on the day of vaccination, followed by a second peak 8 to 12 days later (Fig 5); however, this pattern was most marked for fever, less apparent for rash, and still less so for diarrhea. Median postvaccination day of onset was day 9 for fever, day 5 for diarrhea, day 10 for rash, and day 6 for illness involving any of these symptoms. The majority of toddlers had symptoms lasting only a few days: median days of duration were 2 for fever, 5 for diarrhea, 4 for rash, and 5 for illness involving any of these symptoms (Fig 6). Of those with fever in the 2 weeks after vaccination, the median maximum temperature was 38.6°C (101.5°F; Fig 7). The 33 toddlers with high fever (≥39.5°C [103.1°F]) constituted 19% of those with fever (173) and 6% of the total group 1 population (535). Intensity of fever did not significantly differ when the 173 toddlers with fever in the 2 weeks postvaccination were com-

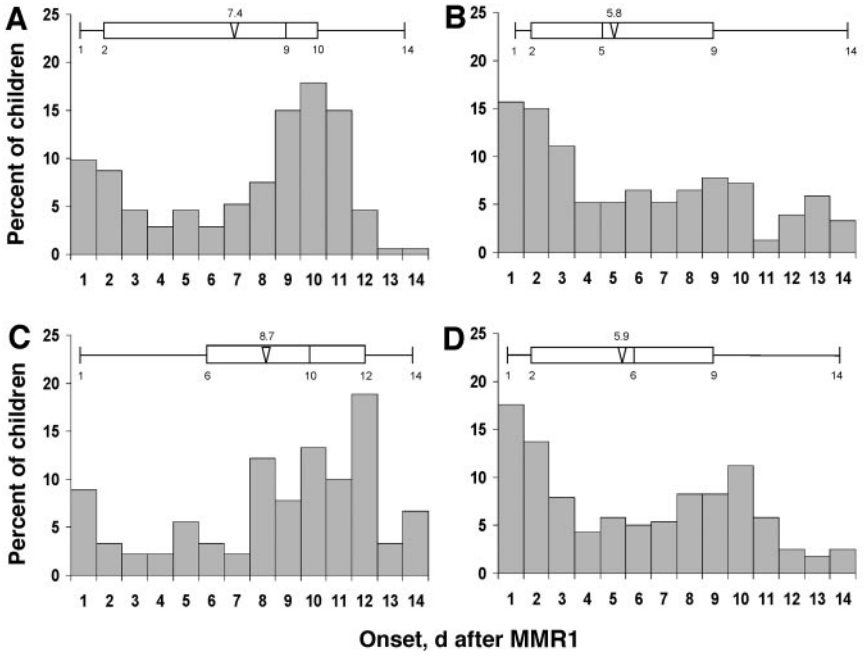

FIGURE 5
Symptom onset. X-axis shows days after vaccination, with day of vaccination the first day. Y-axis shows percentage of children. Only toddlers receiving MMR1 who had a specified symptom during a postvaccination week in which the rate for that symptom was significantly elevated over baseline are included in each graph. A, Fever ($N = 173$); B, diarrhea ($N = 153$); C, rash ($N = 90$); D, fever, diarrhea, or rash ($N = 278$). Bars, percentage of these children who had onset of the symptom for each postvaccination day indicated on the x-axis. In each graph, the bar-and-whisker graphic indicates the minimum, 25th percentile, median, 75th percentile, and maximum. ▽, mean.

pared with the 41 toddlers with fever during the baseline week. The toddlers who received MMR alone (31 [11%]) also had a bimodal pattern of symptom onset; compared with those who received MMR simultaneously with other vaccines (247 [89%]), they did not differ significantly in symptom onset, duration, and fever intensity.

DISCUSSION

We report a study of adverse events associated with the first and second doses of MMR administered at the most common ages for MMR vaccination in the United States. We found that ~18% of children who received MMR1 at 12 to 20 months of age had symptoms of fever, rash, or diarrhea that were probably vaccine associated, with a median onset 5 to 10 days after vaccination and a median symptom duration of 2 to 5 days. However, we also found that fever, rash, or diarrhea occurred so commonly among toddlers in the absence of vaccination that only 34% of all children with such symptoms in the 2 weeks after receipt of MMR1 were likely to have experienced a vaccine-associated adverse event. Our findings

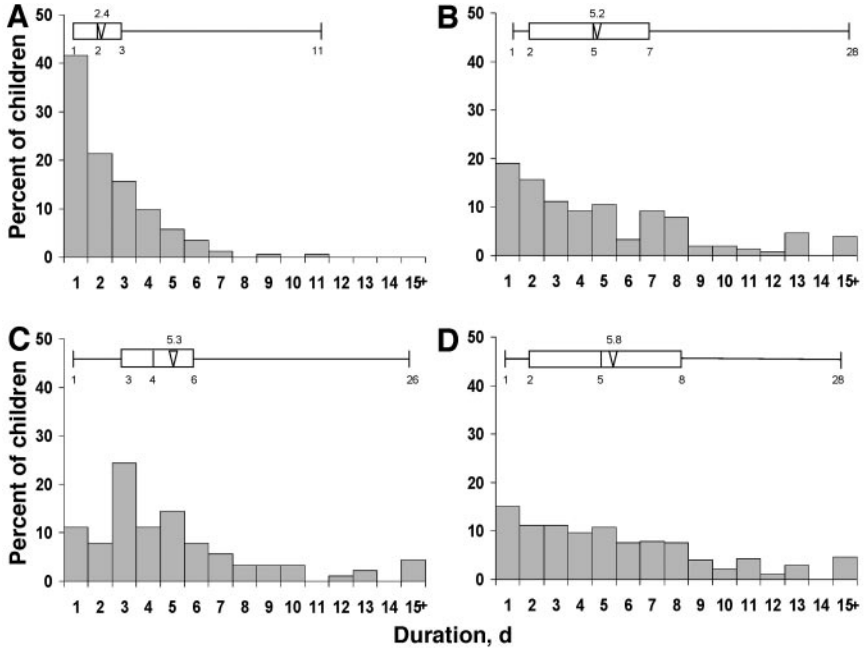

FIGURE 6
Symptom duration. X-axis shows duration in days of each symptom, with day of vaccination the first day. Y-axis shows percentage of children. Only toddlers receiving MMR1 who had a specified symptom during a postvaccination week in which the rate for that symptom was significantly elevated over baseline are included in each graph. A, Fever ($N = 173$); B, diarrhea ($N = 153$); C, rash ($N = 90$); D, fever, diarrhea, or rash ($N = 278$). Bars, percentage of these children whose symptoms lasted the number of days indicated on the X-axis. In each graph, the bar-and-whisker graphic indicates the minimum, 25th percentile, median, 75th percentile, and maximum. ▽, mean.

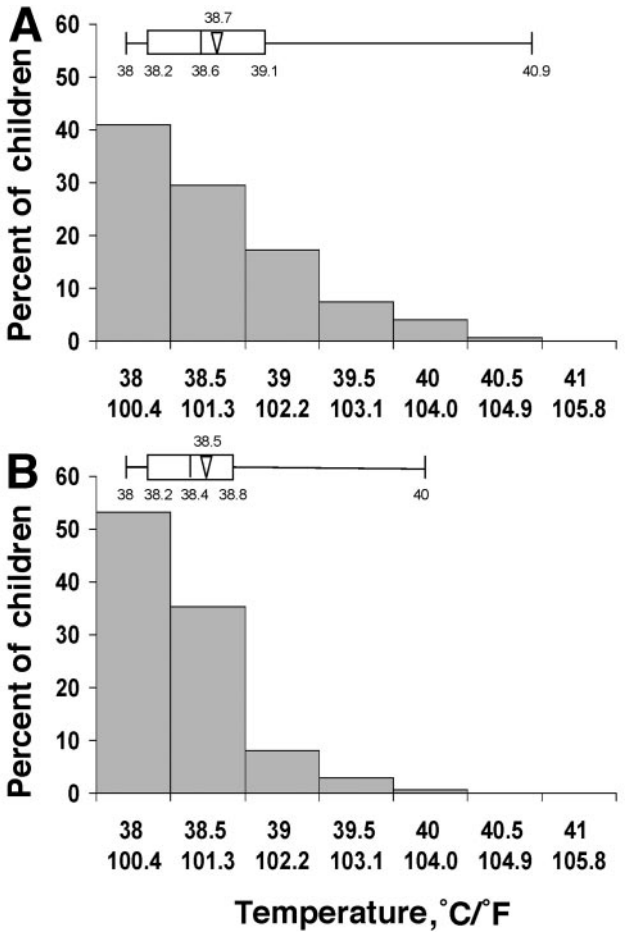

FIGURE 7

Fever intensity. X-axis shows the upper bound of each temperature interval. Y-axis shows percentage of children. Only the 173 toddlers receiving MMR1 who had fever during a postvaccination week in which the rate for that symptom was significantly elevated over baseline are included in each graph. A, maximum temperature; B, average temperature. Bars, percent of these children who had fever within the intervals indicated on the x-axis. In each graph, the bar-and-whisker graphic indicates the minimum, 25th percentile, median, 75th percentile, and maximum. ▽, mean.

confirm and extend those of previous studies and suggest that MMR1 may be among the more reactogenic vaccines in the routine schedule.[11,14]

We were unable to detect any adverse events for children receiving MMR2 when administered at either 4 to 6 years or 10 to 12 years of age. Thus, our study does not demonstrate an advantage for either kindergarten or middle school in the timing of MMR2 administration, suggesting that issues of disease protection and immunogenicity may be more important in the choice of an age for the second dose. Baseline rates of fever, rash, and diarrhea were low (<5%) in both groups of children, and increases did not generally occur post-MMR2; for example, the proportion of children with fever was slightly lower 2 weeks after vaccination than 2 weeks before. These data suggest that MMR2 reactogenicity may be quite low, even in a context where the first dose had been administered as long as 10 years prior, and wild disease boosting is unlikely to have occurred in the interval. Because MMR is a live attenuated vaccine, an immune host is less likely than a nonimmune host to experience vaccine virus replication, perhaps explaining the lowered rate of adverse events among recipients of the second dose compared with the first.

In their prospective placebo-controlled twin study, Peltola and Heinonen[11] and Virtanen et al[14] may have found somewhat lower rates of adverse events for MMR1 than we did, although their analysis is based on child days, and direct comparisons to our findings are difficult. The number and age range of children who received MMR2 is also not clear in their study, but they came to a conclusion consistent with ours about "the virtual nonreactogenicity of the second dose of MMR in previously immunized children."

In their retrospective electronic record review, Davis et al[13] found that of 26 548 children enrolled in a health maintenance organization, 99 made visits for health events potentially related to MMR2 in the month after vaccination compared with 95 during a prevaccination baseline month. These findings are also suggestive of low MMR2 reactogenicity. However, whereas children aged 4 to 6 and 10 to 12 years had identical postvaccination visit rates, the older children made fewer visits at baseline, suggesting to the authors "a greater risk for adverse clinical events after MMR2 immunization among 10- to 12-year-olds than among 4- to 6-year-olds."[13] We are unable to confirm this risk, but primary outcomes differed: our study focused on self-reported symptoms, theirs on documented medical encounters. The low rate of visits (<0.4%) in their large, retrospective record review suggests why we may not have detected any visits in our smaller prospective study. All of the participants in our study had access to a study nurse for discussion of health events, probably reducing the likelihood of a medical encounter, particularly for postvaccination rashes, which accounted for almost half of all of the visits in their study.

A significant postvaccination decrease in respiratory symptoms was observed in our study, which was not apparently attributable to seasonality. Most of the decline occurred at the end of the 4-week postvaccination observation period, raising questions as to whether the apparent improvement continued thereafter. These symptoms were quite common at baseline, and progressive "diary fatigue" may account for some decrease, but such fatigue was not observed for the recording of other common symptoms. Reductions in respiratory symptoms were also found in the Finnish twin study,[14] and the authors concluded that "MMR vaccine might, in fact, give some transient protection from the common cold." Unfortunately for this hypothesis, the trend toward protection in our study seems to have begun before vaccine was administered. In addition, children receiving MMR2 in our study experienced the respiratory benefits more

often than those receiving MMR1, making it difficult to invoke a biological explanation based on the protective value of vigorous immune response. The clearest feature of the respiratory symptom reduction in our study is the problematic nature of inferring causal relationships from incidental findings.

Our study suffers from a number of limitations. Data on adverse events were based on unverified, family recorded symptom diaries. We had no unvaccinated control group. The baseline period for the study subjects lasted only 1 week and was relatively close to vaccination when the "healthy vaccinee effect"[14] may well have been present. A 17% attrition rate occurred, mostly during the baseline diary period. The sample size was inadequate to examine rare adverse events or common adverse events with less than a twofold increase over baseline. The study population was atypical of the overall population of US children, in that they were almost all white, rural, healthy, and received vaccinations at the recommended ages. Other vaccines were administered simultaneously with MMR for >80% children in the 2 younger groups and <1% in the oldest group, making attribution of adverse events and comparison of groups more difficult.

Nevertheless, we believe our study findings confirm that vaccine-associated adverse events occur in ~1 of every 6 toddlers receiving the first dose of MMR, with high fever occurring in ~1 in 20, although very few of these events require medical attention. When the second dose of MMR is administered to school-aged children, adverse events are infrequent and difficult to detect.

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