The Journal of Infectious Diseases

MAJOR ARTICLE

Tolerability of Early Measles-Mumps-Rubella Vaccination in Infants Aged 6–14 Months During a Measles Outbreak in The Netherlands in 2013–2014

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Background. In 2013–2014, a measles outbreak spread through the Netherlands. To protect young infants, measles-mumps-rubella (MMR) vaccination was offered to those aged 6–14 months in municipalities with routine first-dose MMR vaccine coverage of <90%. We assessed the tolerability of this early administration of MMR vaccine.

Methods. After study entry (n = 1866), parents of eligible infants (n = 10 097) completed a questionnaire (n = 1304). For infants who received an early MMR vaccine dose (n = 962), we asked for information about adverse events (AEs) associated with the dose. AE frequencies were compared between infants aged 6–8, 9–11, and 12–14 months. Using multivariable logistic regression, we assessed the association between the risk of AEs and age at early MMR vaccination.

Results. The response rate was 13%. Parents of 59 infants (6.1%) and 350 infants (36.4%) who received early MMR vaccination reported local and systemic AEs, respectively. Parents of infants vaccinated at 6–8 months of age reported systemic AEs less frequently (32%) than parents of children vaccinated at 9–11 months (45%) and 12–14 months (43%) of age ($P = <.001$). For local AEs, there were no differences (5%, 7%, and 10%, respectively; $P = .08$). Compared with vaccination at 6 months, all older infants except those aged 14 months showed an increased risk for any AE and for systemic AEs starting 5–12 days after vaccination.

Conclusions. Early MMR vaccination is well tolerated, with the lowest AE frequencies found in infants aged 6–8 months. It is a safe intervention for protecting young infants against measles.

Keywords. measles; vaccination; tolerability; early MMR; infants; 6 months; outbreak.

Measles is a highly contagious infectious disease, with the most-severe cases occurring in young infants and adults [1]. Measles vaccination was introduced in the National Immunization Program in the Netherlands in 1976. Since 1987, measles vaccination is given in a combined measles-mumps-rubella (MMR) vaccine at 14 months and 9 years of age, with corresponding coverage amounting to 96% (for the first routine dose [MMR1]) and 93% (for MMR1 and MMR2 combined) [2].

During 2013–2014, a measles outbreak spread across the Netherlands, mainly among orthodox Protestants living in sociogeographically clustered communities with a low acceptance of vaccination [3]. Between May 2013 and March 2014, nearly 3000 cases of measles were reported (T. Woudenberg, unpublished data). A previous outbreak among the same group occurred in 1999–2000, with >3200 registered cases [4].

To protect infants in high-risk areas who are younger than the age at which routine MMR vaccination is recommended, all infants aged 6–14 months living in municipalities with MMR1 vaccine coverage of <90% were invited for an early MMR vaccination. Current vaccination guidelines in the Netherlands advise vaccination of infants aged ≥6 months when there is an increased risk to contract measles, such as when travelling to a country where measles is endemic [5]. This is similar to guidelines in the United States [6].

Worldwide, MMR vaccines are licensed for use in individuals aged ≥12 months, while in outbreak settings they can be used beginning at 9 months of age. Concordant with the European Medicines Agency's Summary of Product Characteristics, infants receiving MMR vaccination before 12 months of age are offered a second MMR vaccination after the age of 1 year because of the vaccine's beneficial effects on the cellular and humoral immune response against measles virus [7]. Irrespective of early MMR vaccination, in the Netherlands all children are offered another dose of MMR vaccine at the age of 9 years. The advice to vaccinate infants aged ≥6 months was based on Dutch population-based seroprevalence data from 1995–1996 and 2006–2007, combined with evidence on age-specific

Received 28 September 2015; accepted 14 December 2015; published online 21 December 2015.

Presented in part: 32nd Annual Meeting of the European Society for Paediatric Infectious Diseases, Dublin, Ireland, 6–10 May 2014.

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The Journal of Infectious Diseases® 2016;213:1466–71

DOI: 10.1093/infdis/jiv756

immunogenicity and effectiveness [8–11]. The seroprevalence data suggested that most infants aged ≥6 months lacked maternal antibodies, especially when they were born to vaccinated mothers.

MMR vaccination at ages ≥6 months is regarded as safe, based on studies mainly performed during vaccination campaigns in developing countries [12–15]. Some studies also show beneficial effects due to a reduced overall mortality rate after early measles vaccination [16]. In the light of continuing measles outbreaks in developed countries and the need to comply with World Health Organization targets for eliminating measles and rubella, information on the effectiveness, safety, and impact of early MMR vaccination gives valuable input to policy makers responsible for outbreak control measures. In this article, we describe and discuss results of the tolerability of MMR vaccine received during a campaign to deliver MMR vaccine at early ages in the Netherlands.

METHODS

Setting and Participants

In response to the measles outbreak among orthodox Protestants, an outbreak management team decided on 17 June 2013 to offer early MMR vaccination to all infants aged 6–14 months who were living in municipalities with MMR1 vaccine coverage of <90%. On 13 July 2013, parents of eligible infants received a personal invitation for early MMR vaccination through the routine vaccination program register. The Netherlands has a very complete national vaccination registration, which allows direct targeting of additional vaccination to risk groups [17]. Thereafter, all parents of infants turning 6 months of age in the previous week and residing in the eligible municipalities received an invitation for early MMR vaccination of their infant. Last invitations were distributed in week 8 of 2014. To avoid interference with the willingness to vaccinate, invitations to participate in our study were sent 4 weeks after the invitation for vaccination. Parents willing to participate could return an application form with their e-mail address. In return, they received a link to an online questionnaire. Parents who indicated in the past that they did not want to receive regular mail from the vaccination registry were not invited to participate in our study.

For this study, institutional review board approval was not necessary because only questionnaire data were used and infants are not subjected to procedures and are not required to follow rules of behaviour. This was confirmed by the Central Committee on Research Involving Human Subjects of the Netherlands.

Vaccine

The vaccine administered during this vaccination campaign was identical to the MMR vaccine used in the National Immunization Program at 14 months and 9 years of age at that time (MMRvaxpro; Sanofi Pasteur MSD). This vaccine contains at least 1×10^3 50% cell culture infectious doses ($CCID_{50}$) of the Enders Edmonston strain of measles virus, 12.5×10^3 $CCID_{50}$ of the Jeryl Lynn strain of mumps virus, and 1×10^3 $CCID_{50}$ of the Wistar RA 27/3 strain of rubella virus; all are live attenuated strains. Measles and mumps virus strains are produced in chick embryo blasts, whereas the rubella virus strain is produced in WI-38 human diploid lung fibroblasts. The vaccine is given subcutaneously in the upper arm.

Data Collection

The online questionnaire asked for demographic characteristics of the infant eligible for early MMR vaccination and of the entire household. Furthermore, past and present measles virus infections and the vaccination status of all household members were ascertained. If early MMR vaccination occurred, questions about local and systemic adverse events (AEs) were asked, with details on severity, time since vaccination, and duration of symptoms. Tolerability data were only available for infants who received early MMR vaccination before parents completed the first questionnaire.

Outcome Definitions

Local AEs were classified as mild, moderate, or pronounced. Systemic AEs were dichotomized. We defined fever as a temperature of ≥38.0°C, measured sublingually, intra-auricularly, or rectally, based on the Brighton Collaboration case definition [18]. Very high fever was defined as a temperature of ≥40.5°C. The interval between early MMR vaccine receipt and the day of onset of systemic AEs was divided into 3 periods (ie, days 0–4, 5–12, or ≥13).

Covariates

All covariates were retrieved from the questionnaire. If parents permitted, their infant's vaccination status was checked in the national vaccination register. All other covariates were self-reported without validation.

Statistics

Frequencies and means of demographic values, local AEs, and systemic AEs are presented overall and stratified by age (ie, 6–8 months, 9–11 months, and 12–14 months). Differences were tested using the Pearson χ^2 or Fisher exact tests (for dichotomous and categorical variables) or the Student *t* test (for continuous variables).

We calculated the mean and median times between vaccination and completion of the questionnaire, both overall and after stratification into the 3 age groups. To assess whether this interval influenced the reported frequencies of AEs, we divided the participants into a group that completed the questionnaire early after vaccination (ie, the group with an interval below the median interval; hereafter, "early responders") and a group with an interval similar to or longer than the median interval (hereafter, "late responders").

To assess whether age at the time of early MMR vaccination was associated with the risk of any AE (ie, local or systemic AEs

in any risk interval) or with systemic AEs starting 5–12 days after early MMR vaccination, we performed multivariable logistic regression, with age was categorized in months. Covariates with a plausible or known effect on the outcome (ie, sex, underlying disease of the infant, any history of breastfeeding, gestational age, older siblings in the household, maternal age and educational level, measles vaccination status, past measles virus infection of the mother, and reasons for refusing past vaccination) were included as possible confounders in the multivariable model (Table 1). By use of stepwise backward selection, all covariates with an influence of <10% on the estimate of the main determinant (ie, age in months) were discarded from the model. We also assessed possible interactions. Risks are presented as odds ratios (ORs) with 95% confidence intervals.

Analyses were performed using SAS, version 9.3. In all analyses, a *P* value of <.05 was considered statistically significant.

RESULTS

Response

In total, 10 097 infants in all 29 municipalities with MMR1 vaccine coverage of <90% in 2012 were invited to receive early MMR vaccination. Of these, parents of 9974 infants were invited to participate in the study (for 123 infants, the address was not available or parents had indicated that they did not want to receive regular mail from the vaccination registry). Parents of 1866 infants (19%) responded. Finally, parents of 1304 infants (13%) completed the first questionnaire. By the time parents completed the first questionnaire, 962 infants (74%) had already received an early MMR vaccine dose. We report tolerability data for these 962 infants.

The median interval between early MMR vaccination and completion of the questionnaire was 49 days (mean, 51.4 days; range, 1–211 days). The median interval was 44 days (mean, 48.7 days; range, 1–211 days) for infants aged 6–8 months, 57.2 days (mean, 55 days; range, 9–148 days) for infants aged 9–11 months, and 51 days (mean, 53.3 days; range, 8–144 days) for infants aged 12–14 months. Differences in the median intervals among the 3 age groups were statistically significant ($P < .0001$).

Demographic Characteristics

The median age at early MMR vaccination was 7.0 months (range, 5.7–14.9 months). In total, 603 infants (62.7%) received their early MMR vaccination at the age of 6–8 months (median, 6.3 months), whereas 239 (24.8%) and 120 (12.5%) received their early MMR vaccination at age 9–11 months (median, 10.0 months,) and 12–14 months (median, 12.7 months), respectively. An equal number of boys and girls (481 each) received early MMR vaccination during this campaign. Sex distribution between the 3 age groups were equal ($P = .3$; Table 1). Furthermore, we found no differences between the age groups in day care attendance, underlying disease in the infant, duration of pregnancy, presence of older siblings, vaccination refusal on the basis of life philosophy (eg, anthroposophy, homeopathy, or alternative medicine) or religion, maternal educational level, maternal vaccination status, and past maternal measles virus infection. In contrast, smaller percentages of infants aged 6–8 months ever breastfed ($P = .01$) or had a mother in the oldest age category (ie, >38 years; $P = .02$) than infants in older age groups.

Table 1. Background Characteristics of Participants, by Age at Receipt of the Early Measles-Mumps-Rubella Vaccine

Characteristic	6–8 mo, No. (%) (n = 603)	9–11 mo, No. (%) (n = 239)	12–14 mo, No. (%) (n = 120)	*P* Value
Day care attendance				
Yes	404 (67.0)	158 (66.1)	79 (65.8)	.9
Ever breastfed				
Yes	427 (70.8)	188 (78.7)	97 (80.8)	.01
Underlying disease in infant				
Yes	44 (7.3)	9 (3.8)	12 (10.0)	.06
Sex				
Male	301 (49.9)	113 (47.3)	67 (55.8)	.3
Female	302 (50.1)	126 (52.7)	53 (44.2)	
Duration of pregnancy, wks				
37–44	567 (94.0)	228 (95.4)	109 (90.8)	.6
32–36	28 (4.6)	9 (3.8)	9 (7.5)	
26–31	6 (1.0)	2 (0.8)	2 (1.7)	
Unknown	2 (0.3)	0	0	
Other siblings in household				
Yes	330 (54.7)	123 (51.5)	73 (60.8)	.2
Vaccination refused on the basis of life philosophy or religion				
No	544 (90.2)	212 (88.7)	100 (83.3)	.2
Moderate	58 (9.6)	26 (10.9)	20 (16.7)	
Strong	1 (0.2)	1 (0.4)	0	
Maternal year of birth				
1986–1995	113 (18.7)	40 (16.7)	17 (14.2)	.02
1976–1985	444 (73.6)	168 (70.3)	86 (71.7)	
1966–1975	37 (6.1)	26 (10.9)	17 (14.2)	
Unknown	9 (1.5)	5 (2.1)	0	
Maternal educational level				
No education or only primary/secondary school	50 (8.3)	24 (10.0)	7 (5.8)	.5
Intermediate vocational education	230 (38.1)	98 (41.0)	51 (42.5)	
Higher vocational education or university	316 (52.4)	113 (47.3)	62 (51.7)	
Unknown	7 (1.2)	4 (1.7)	0	
Maternal vaccination status				
Unvaccinated	39 (6.5)	23 (9.6)	5 (4.2)	.3
Vaccinated	511 (84.7)	194 (81.2)	103 (85.8)	
Unknown	53 (8.8)	22 (9.2)	12 (10.0)	
Past maternal measles virus infection				
No	405 (67.2)	153 (64.0)	69 (57.5)	.2
Yes	81 (13.4)	32 (13.4)	17 (14.2)	
Unknown	117 (19.4)	54 (22.6)	34 (28.3)	

Local AEs

Parents of 59 infants (6.1%) reported ≥1 local AE following the early MMR vaccination (Table 2). There was a trend of an

Table 2. Absolute Numbers and Frequencies of Local and Systemic Adverse Events (AEs) After Measles-Mumps-Rubella Vaccine Receipt, Overall and by Age

AE	6–8 mo, No. (%) (n = 603)	9–11 mo, No. (%) (n = 239)	12–14 mo, No. (%) (n = 120)	*P* Value[a]	Overall, No. (%) (n = 962)
Local					
Any	30 (5)	17 (7)	12 (10)	.08	59 (6)
Redness	26 (4)	15 (6)	12 (10)	.58	53 (6)
Pain	21 (3)	13 (5)	6 (5)	.15	40 (4)
Swelling	15 (2)	11 (5)	7 (6)	.67	31 (3)
Systemic					
Any	191 (32)	108 (45)	51 (43)	.0004	350 (36)
Listlessness	149 (25)	87 (36)	38 (32)	.68	274 (28)
Fever	106 (18)	68 (28)	25 (21)	.22	200 (21)
Crying	98 (16)	59 (25)	28 (23)	.82	185 (19)
Rash	46 (8)	48 (20)	22 (18)	.0004	116 (12)
Sleeping problems	52 (9)	27 (11)	15 (13)	.83	94 (10)
Diarrhea	17 (3)	10 (4)	4 (3)	.96	31 (3)
Vomiting	12 (2)	7 (3)	2 (2)	.79	21 (2)
Paleness	11 (2)	7 (3)	2 (2)	.81	20 (2)

[a] For the difference between age groups.

increasing frequency of local AEs with increasing age, but differences were not statistically significant ($P = .08$). We found no difference in the frequency of any local AE between the early and the late responders in the overall study population ($P = .09$), as well as by age group ($P = .2$, $P = .5$, and $P = .6$ for infants aged 6–8 months, 9–11 months, and 12–14 months, respectively). Redness (53 infants [5.5%]) was reported most often, followed by pain (40 [4.2%]) and swelling (33 [3.4%]). Redness, pain, and swelling started within 24 hours after vaccination in 72%, 80%, and 82% of infants, respectively, whereas symptoms lasted <3 days in 72%, 75%, and 70%, respectively. Parents of 8 infants (0.1%), 6 (0.1%), and 4 (0.07%) reported pronounced redness, pain, and swelling, respectively.

Systemic AEs

Parents of 350 infants (36.4%) reported ≥1 systemic AE (Table 2). Parents of infants who were 6–8 months old at the time of early MMR vaccination reported systemic AEs less frequently than those of infants in older age groups ($P < .001$). Overall frequencies were 31.7% (n = 191), 45.5% (n = 108), and 42.5% (n = 51) for those aged 6–8, 9–11, and 12–14 months, respectively. We found no difference in the frequency of any systemic AE between the early and the late responders in the overall study population ($P = .1$) and in the infants aged 12–14 months ($P = .3$). Among the infants aged 6–8 months, the frequency of any systemic AE was higher in the early responders than in the late responders (52.8% vs 47.2%; $P = .05$). Likewise, among the infants aged 9–11 months, 56.9% of early responders reported any systemic AE, compared with 43.1% of late responders ($P = .04$). No differences in the frequencies of specific systemic AEs were found between age groups, except for rash, which occurred less frequently among infants aged 6–8 months (8%), compared with those aged 9–11 months (20%) or 12–14 months (18%).

Listlessness (274 infants [28%]) was reported most often, followed by fever (182 [19%]), crying (185 [19%]), rash (116 [12%]), and sleeping problems (94 [10%]). Parents of 2 infants reported fever with a temperature of ≥40.5°C. For one of these infants, fever started within the risk window 5–12 days after vaccination. Among the systemic AEs, most (range, 62%–75% of cases, depending on the AE) started 5–12 days after the vaccination. A minority of parents reported a start of symptoms within 4 days after vaccination (range, 13%–26%, depending on the systemic AE) or >12 days after vaccination (range, 5%–24%). In 30%–69% of cases, depending on the systemic AE, the duration of symptoms was ≤2 days, whereas in 15%–26% and 16%–50%, symptoms lasted 3 days or ≥4 days, respectively.

Influence of Age at Time of Early MMR Vaccination on Occurrence of Local and Systemic AEs

After entering all possible confounders in the multivariable logistic regression, for both outcomes stepwise backward selection led to removal of all covariates (ie, no adjustment was necessary). With 6-month-old infants set as reference, ORs for all older ages were >1 (range, 1.1–2.7 and 1.4–4.0 for any AE and for systemic AEs 5–12 days after vaccination, respectively), except for 14-month-old infants (ORs, 0.5 and 0.8 for local and systemic AEs, respectively; Table 3). For any AE, ORs were not statistically significant in infants aged 8 months and those aged 14 months, whereas for systemic AEs occurring 5–12 days after vaccination, ORs were nonsignificant in infants aged 7, 8, 12, or 14 months.

DISCUSSION

To our knowledge, this is the first study that assessed the tolerability of MMR vaccination administered at ages ≥6 months in a developed country. We showed that this early MMR vaccination was well tolerated and that AEs in infants receiving their first MMR vaccine dose at 6–8 months of age were less frequent than AEs in infants aged 14 months, the age when routine MMR1 vaccination is scheduled in the Netherlands.

We found that the occurrence of AEs is age dependent. Frequencies of all local and most systemic AEs were lower in the youngest age group of 6–8 months, compared with older age groups. For both local as well as most systemic AEs, frequencies were lowest in the youngest age category. For fever and rash, we found frequencies of 15% and 7%, respectively, among infants aged 6 months; 20% and 20%, respectively, among infants aged 9 months; and 24% and 15%, respectively, among infants aged 12 months. However, only the frequencies of rash and all systemic AEs combined differed statistically significant between

Table 3. Logistic Regression Analysis of Risk of Any Adverse Event (AE) and of Systemic AEs 5–12 Days After Early Measles-Mumps-Rubella (MMR) Vaccination, by Age at Early MMR Vaccination

		Any AE		Systemic AE 5–12 d After Vaccination	
Age, mo	Infants, No.	Yes, No. (%)	OR (95% CI)	Yes, No. (%)	OR (95% CI)
6	388	120 (31)	Reference	76 (20)	Reference
7	123	51 (41)	1.58 (1.04–2.4)	31 (25)	1.38 (.86–2.23)
8	81	27 (33)	1.12 (.67–1.86)	20 (25)	1.35 (.77–2.37)
9	72	31 (43)	1.69 (1.01–2.82)	24 (33)	2.05 (1.18–3.56)
10	81	39 (48)	2.07 (1.28–3.37)	27 (33)	2.05 (1.21–3.47)
11	66	30 (45)	1.86 (1.1–3.16)	20 (30)	1.79 (1–3.19)
12	68	31 (46)	1.87 (1.11–3.16)	18 (26)	1.48 (.82–2.68)
13	55	30 (55)	2.68 (1.51–4.75)	27 (49)	3.96 (2.21–7.11)
14	12	2 (17)	0.45 (.1–2.07)	2 (17)	0.82 (.18–3.83)

Abbreviations: CI, confidence interval; OR, odds ratio.

the age groups. Studies performed in Uzbekistan and Malawi found no influence of age on the occurrence of specific AEs among infants who received measles–containing vaccines at 6 and 9 month of age [12, 13]. Bolotovski et al found frequencies of fever and rash (6%–14%) that were similar to ours after administration of several measles vaccines differing in strain and potency to infants aged 6 months (n = 1202) and 9 months (n = 1250) [13]. AEs were reported during an interview in the home in the second week after vaccination. In the study by Helfand et al [12], proportions of human immunodeficiency virus (HIV)–unexposed control subjects with fever and rash following measles vaccination (14% and 1%, respectively, among infants aged 6 months [n = 512] and 11% and 1%, respectively, among those aged 9 months [n = 572]) were somewhat lower than those in our study. In the study by Helfand et al, parents recorded AEs in a daily log for 21 days after vaccination. The differences between the frequencies of AEs in these studies and the frequencies in our study may be attributed to varying methods of AE ascertainment. Furthermore, Bolotovski et al and Helfand et al presented no case definition of or cutoff temperature for fever, possibly leading to different numbers of cases with fever, which perhaps partly explains the differences.

In a study of German infants who received MMR vaccine, 70% aged 9–11 months (n = 43) and 76% aged 12–14 months (n = 29) reported fever [19]. This is much higher than the frequencies we found (28% and 21%, respectively), but these differences are difficult to interpret because of the small sample size of the German study.

Another possible explanation for the lower frequencies of AEs in younger infants is the presence of maternal antibodies against measles virus that prohibit replication of vaccine virus and thereby prevent the occurrence of AEs. Dutch seroprevalence data showed that, in the general population, immunoglobulin G antibody levels were below the cutoff for protection in 54% of 3-month-old infants (95% confidence interval, 34%–74%) [9]. Among children born to orthodox reformed Protestant mothers who in general were naturally infected, the duration of protection was approximately 2 months longer [10]. Furthermore, breastfeeding, maternal vaccination status, and past measles virus infection of the mother were included in the multivariable regression analysis but did not influence the main estimate by >10% and were therefore not considered as confounders. Therefore, we think the influence of maternal antibodies is limited. However, we cannot exclude a possible influence of nondetectable, residual maternal antibodies. Furthermore, young infants are immunologically immature, which may also lead to less reactogenicity.

Two other Dutch surveys on the tolerability of MMR1 vaccination given at age 14 months found different frequencies of local and systemic AEs than we observed among infants aged 12–14 months in our study [20, 21]. Kroesbergen et al (n = 863) found local reactions among 9%, fever among 32%, crying among 38%, and rash among 24% [20], while Jongerius et al (n = 391) found frequencies of 24%, 20%, 17%, and 17%, respectively [21]. In our study, frequencies were 10% for local reactions, 14% for fever, 18% for crying, and 13% for rash. The lower frequencies we found may be explained by study logistics: study participation was requested 4 weeks after the invitation for vaccination, and parents of infants who received the vaccination before completion of the survey might not have remembered all AEs, particularly the less severe symptoms. Another possible explanation for the lower frequency of AEs found in our study is that our primary aim was to assess vaccine effectiveness, with additional questions on AEs, while both MMR1 surveys exclusively assessed tolerability. Therefore, the frequencies we found were probably less likely to have been affected by overreporting, compared with the 2 tolerability surveys.

Apart from this survey, parents were asked to report AEs after vaccination to the Dutch Pharmacovigilance Center, Lareb. Lareb received 11 reports, of which 2 involved serious systemic AEs (1 infant had febrile convulsion and 1 experienced crying and dehydration).

Our study has several limitations. First, only 13% of the parents of eligible infants completed the questionnaire, which may hamper generalizability. However, the overall early MMR vaccination coverage in the 29 municipalities was 66%, while 74% of the infants in our study received early MMR vaccination. These percentages do not differ very much. Therefore, we think the risk of bias is low, despite the low response rate. Furthermore, the sex distribution in our study is comparable to the distribution in the general population.

The overall median interval between early MMR vaccination and questionnaire completion was >1.5 months. This possibly influenced the reported AEs, resulting in an underestimation. However, because the age group in which this interval was shortest also had the lowest AE frequencies, recall bias may be limited.

Because this outbreak occurred in a high-income country, results may be less applicable to developing countries. The latter countries often have a less developed healthcare system and a greater prevalence of malnutrition, possibly (1) resulting in an impaired immune response and (2) influencing the occurrence of AEs.

Furthermore, all AEs were self-reported without additional validation. This may have led to an overestimation of AE frequencies. As known from the twin study by Peltola et al on MMR vaccine–associated AEs, the vast majority of AEs following MMR vaccination are temporally associated but not causally related [22]. Therefore, most AEs reported in our study were probably not caused by MMR vaccination. Since we did not compare results with the occurrence of symptoms in age-matched unvaccinated children, we could not assess causality. We also were unable create an internal control group by monitoring the occurrence of the AEs prior to vaccination, because we sent invitations to participate 4–5 weeks after the invitation for vaccination so that there would be no interference with parent's decision regarding the vaccination. However, the rates found are useful for monitoring variation in AE frequencies between groups and over time and an efficient and easy way to monitor tolerability.

To conclude, our results show that early MMR vaccine administration during an outbreak is safe to protect infants aged 6–14 months against measles. Frequencies of local and common systemic AEs were lowest in younger age classes.

Notes

Financial support. This work was supported by the Dutch government.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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