



## Outbreak of Aseptic Meningitis associated with Mass Vaccination with a Urabe-containing Measles-Mumps-Rubella Vaccine

### Implications for Immunization Programs

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A mass immunization campaign with a Urabe-containing measles-mumps-rubella vaccine was carried out in 1997 in the city of Salvador, northeastern Brazil, with a target population of children aged 1–11 years. There was an outbreak of aseptic meningitis following the mass campaign. Cases of aseptic meningitis were ascertained through data collected from the records of children admitted to the local referral hospital for infectious diseases between March and October of 1997, using previously defined eligibility criteria. Vaccination histories were obtained through home visits or telephone calls. Eighty-seven cases fulfilled the study criteria. Of those, 58 cases were diagnosed after the vaccination campaign. An elevated risk of aseptic meningitis was observed 3 weeks after Brazil's national vaccination day compared with the risk in the prevaccination period (relative risk = 14.3; 95% confidence interval: 7.9, 25.7). This result was confirmed by a case series analysis (relative risk = 30.4; 95% confidence interval: 11.5, 80.8). The estimated risk of aseptic meningitis was 1 in 14,000 doses. This study confirms a link between measles-mumps-rubella vaccination and aseptic meningitis. The authors discuss the implications of this for the organization and planning of mass immunization campaigns. *Am J Epidemiol* 2000;151:524–30.

disease outbreaks; meningitis, aseptic; mumps vaccine; product surveillance, postmarketing; vaccines

Aseptic meningitis is a well documented adverse event (1–4) that is attributable to the Urabe mumps strain of the combined measles-mumps-rubella (MMR) vaccine. To our knowledge, the occurrence of aseptic meningitis in the form of a typical outbreak following a mass immunization campaign with Urabe- and Lenigrad-Zagreb-containing vaccine has not so far been reported.

A mass immunization campaign with MMR vaccine was started in Brazil in 1992. It began in the state of São Paulo with a nonselective approach (5). Since then, similar campaigns have been conducted in different states of Brazil each year, always with a target population of children aged 1–11 years. In the second

semester (August, September, and October) of 1997, the MMR immunization campaign was carried out in four different states. In three states, the state Epidemiology Surveillance Service was notified of an aseptic meningitis outbreak approximately 15 days after the national vaccination day.

Media coverage of such outbreaks and the potential for a reduction in vaccination compliance in further campaigns has generated concern among public health officers and campaign administrators. We carried out an investigation to estimate the risk of aseptic meningitis associated with MMR vaccine delivered in a mass immunization campaign and to address the implications for Brazil's national immunization program.

### MATERIALS AND METHODS

The study was carried out in Salvador, the capital city of the state of Bahia. It is a city with approximately 2.2 million inhabitants located in northeastern Brazil. In 1997, MMR vaccine was used on a large scale for the first time as part of a mass immunization campaign in Bahia. MMR vaccine had been used previously in private clinics, but only a small proportion of the population had had access to it. The 1997 campaign had the following characteristics: 1) a target

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Abbreviation: MMR, measles-mumps-rubella.

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population with a wide age range of 1–11 years and 2) high coverage reached in a short time period, starting on August 16th, the national vaccination day. The national vaccination day was highly publicized, and 45 percent of the target population was vaccinated on that day. High coverage was achieved during the 2 weeks following the national vaccination day. The estimated target population aged 1–11 years numbered 452,344 according to the 1996 census (6). The national vaccination day fell within the 33rd week of the state Epidemiology Surveillance Service's calendar, which started on December 30 for 1997.

In Salvador, the Pluserix vaccine (Smith-Kline Beecham Pharmaceuticals, London, United Kingdom), which contains the Urabe mumps strain, was used. Vaccination uptake was very close to 100 percent in all age ranges (7). The city has a state referral hospital for infectious diseases (Hospital Couto Maia) which accounts for nearly 90 percent of all notified cases of meningitis that occur in the capital (8).

There were no special arrangements made to implement postmarketing surveillance during the mass immunization campaign by the Bahia State Health Department. The data presented here were obtained from the state Epidemiology Surveillance Service and from ongoing data collection by the hospital neurologic service during 1997. Cases of meningitis were ascertained by prospectively obtaining records of children admitted to the referral hospital from the 10th to the 43rd epidemiologic surveillance weeks, through the cited data sources. Demographic, clinical, and laboratory data were collected from a standardized questionnaire. Vaccination histories were obtained through home visits or telephone calls. Vaccination cards were required, but if they were not available, information that the child had been vaccinated on the national vaccination day was assumed to be reliable for the MMR vaccine, because it was the only vaccine administered by injection that day.

The following criteria were used to define eligible cases of aseptic meningitis for the study: 1) residence in the city of Salvador; 2) age 1–11 years; 3) cerebrospinal fluid with a cell count of  $>10$  and  $<1,200$  cells per ml (higher counts could be attributed to unconfirmed bacterial meningitis); 4) predominance of lymphocytes in the cerebrospinal fluid of  $>50$  percent of the total number of cells; 5) exclusion of any bacteriologic or fungal confirmation through the use of Gram stain, latex, immunoelectrophoresis, stain for *Cryptococcus neoformans*, Ziehl-Neelsen stain, or culture for bacteria and *Mycobacterium tuberculosis*; and 6) exclusion of all cases with a history of prior meningitis or any neurologic disorder and any cases with sepsis, pneumonia, otitis, or any other disease that

might be associated with an increased cell count in the cerebrospinal fluid.

The incidence of aseptic meningitis was calculated before and after the mass immunization campaign. The denominator for the precampaign group was calculated using the estimated target population of children aged 1–11 years who were not vaccinated, multiplied by 23 weeks (the reference period). In view of the high coverage achieved during the 1997 mass immunization campaign, it was assumed that the entire target population was vaccinated. Therefore, the denominator for the incidence of aseptic meningitis by epidemiologic week for the postcampaign group was calculated using the same estimated target population. The numerators were the total numbers of cases in the pre- and postcampaign periods.

Relative risks and attributable fractions were calculated from standard cohort methods. Taylor series approximations of the relative risk variance were used to calculate 95 percent confidence intervals (9). For case children with full vaccination records, time to onset was defined as the period between the day of vaccination and the day of hospital admission.

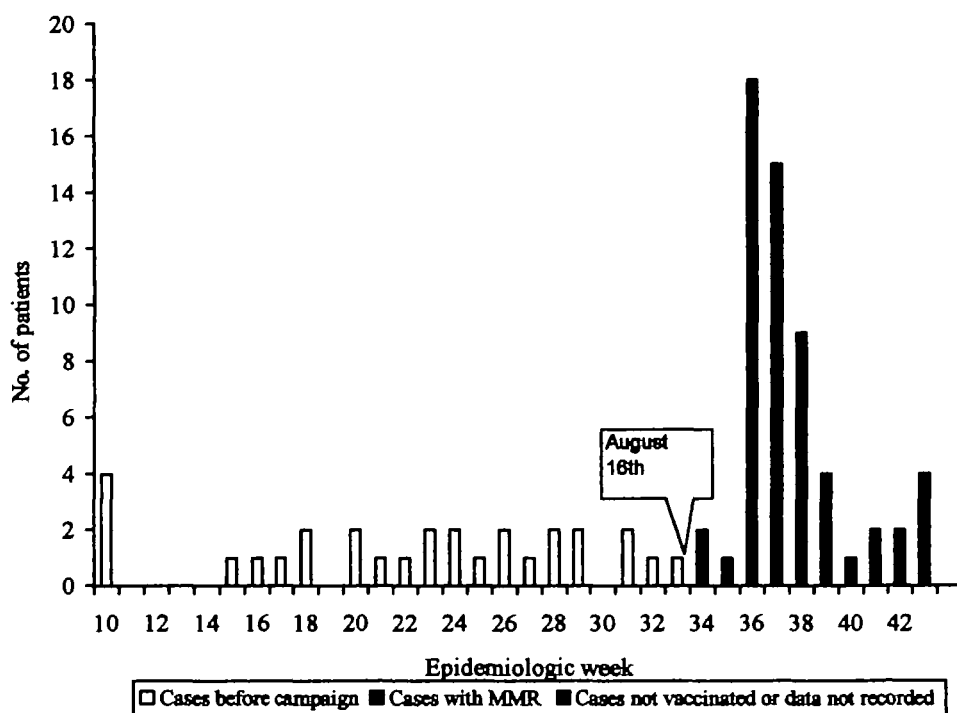
The relative risk calculations were also undertaken with the case series method (10), using only cases presumed to be unvaccinated and cases with complete information on vaccination. We used the 15- to 35-day period following MMR vaccination as the risk period, and controlled for temporal variation in incidence using monthly time intervals. This method makes no assumptions about the denominator population.

To calculate the risk of aseptic meningitis per number of doses of MMR vaccine, the attributable number (9) among exposed cases was used as the numerator and the estimated population at risk was used as the denominator.

## RESULTS

A total of 129 children aged 1–11 years were admitted to the referral hospital with a diagnosis of aseptic meningitis between the 10th and 43rd epidemiologic surveillance weeks of 1997, representing a period from March to October. Of these cases, 87 (67 percent) fulfilled the study criteria for aseptic meningitis. Thirty-three percent (29/87) of the cases occurred prior to the mass immunization campaign. Of the 58 children whose cases were diagnosed after the mass immunization campaign, 50 (86 percent) were known to have been vaccinated with MMR during the 1997 campaign. The date of vaccination was available for 43 of these children.

Figure 1 demonstrates a rapid increase in the number of children with aseptic meningitis admitted to the hospital during the third week (the 36th epidemiologic



**FIGURE 1.** Distribution of cases of aseptic meningitis among children aged 1–11 years following a mass immunization campaign with Urabe-containing measles-mumps-rubella (MMR) vaccine, by epidemiologic week (10th–43rd weeks), Salvador, Brazil, 1997. August 16th was the national immunization day.

surveillance week) after the national vaccination day, with an epidemic curve typical of a point-source outbreak. The number of cases returned to precampaign levels by the 40th epidemiologic week. No sequelae or deaths were observed.

Table 1 shows the incidence rates and relative risks for aseptic meningitis by epidemiologic week. We found an elevated risk of aseptic meningitis in the 36th, 37th, 38th, and 39th epidemiologic weeks in comparison with the prevaccination period. The risk was greatest in the 36th epidemiologic week (relative risk = 14.3; 95 percent confidence interval: 7.9, 25.7), showing an abrupt increase in the number of cases 3

weeks after the national vaccination day. Over the following 3 weeks, though it was still high, the risk gradually declined, returning to prevaccination figures by the 40th epidemiologic week.

These results were confirmed by the case series analysis. Using this method, the relative risk in the period 3–5 weeks after vaccination was estimated as 30.4 (95 percent confidence interval: 11.5, 80.8).

To calculate the attributable fraction, we used only the 37 cases with known vaccination dates occurring in the 36th–39th epidemiologic surveillance weeks. The attributable fraction among the exposed children from the 36th epidemiologic week to the 39th was 86.5 per-

**TABLE 1.** Incidence and relative risk of aseptic meningitis before and after the national day of vaccination with measles-mumps-rubella vaccine, Salvador, Brazil, 1997

Exposure period	No. of cases	Person-weeks of observation	Incidence rate ( $\times 10^{-6}$ )	Relative risk	95% confidence interval
Reference period (10th–33rd epidemiologic surveillance weeks)	29	10,403,912	0.29	1.00	
Epidemiologic week after vaccination day					
34–35	3	904,688	0.33	1.19	0.36, 3.91
36	18	452,344	3.97	14.28	7.93, 25.71
37	15	452,344	3.31	11.90	6.38, 22.19
38	9	452,344	1.98	7.14	3.38, 15.08
39	4	452,344	0.88	3.17	1.12, 9.02
40–43	9	1,809,376	0.49	1.78	0.84, 3.77

cent, which corresponds to 32 cases attributable to the vaccine. Similar results were obtained by the case series method (attributable fraction = 95 percent). We conservatively estimated the risk of aseptic meningitis to be 1 in 14,000 doses (32 cases out of 452,344 applied doses).

The median time to onset among the 43 postcampaign cases with known vaccination dates was 24 days (range, 5–68). Figure 2 suggests that the incubation period of aseptic meningitis is 3–5 weeks after vaccination.

The risk of aseptic meningitis by age group is shown in table 2. Among children who were vaccinated, the incidence rate was lowest among those aged 9–11 years. The estimated relative risk was greatest among children aged 4–8 years (relative risk = 4.5; 95 percent confidence interval: 1.9, 10.6) in comparison with those aged 9–11 years. Among unvaccinated children, the risk was homogeneous across age groups. Males were found to have a higher frequency of aseptic meningitis among both vaccinated children (75 percent (35/47)) and unvaccinated children (80 percent (24/30)).

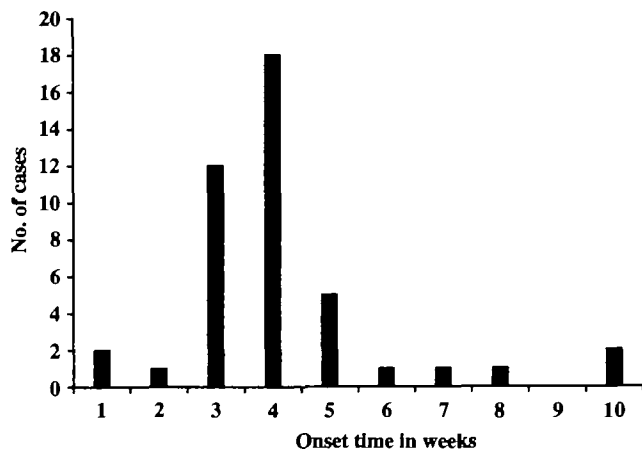


FIGURE 2. Onset times of cases of aseptic meningitis among children aged 1–11 years after vaccination with Urabe-containing measles-mumps-rubella vaccine in a mass immunization campaign, Salvador, Brazil, 1997.

## DISCUSSION

The risk of aseptic meningitis associated with MMR vaccine has been well described, especially concerning Urabe-containing products (1–4, 11, 12), and our results are similar to previous risk estimations (as in the work by Miller et al. (1)) of an incidence of nearly 1 case per 10,000 vaccinees. In spite of previous reports, the Urabe-containing MMR vaccine was previously judged by the Brazilian National Immunization Program to be beneficial for use in a mass immunization campaign, for reasons that included 1) the relative rarity of adverse events, 2) the relative cost and possibly higher immunogenicity in comparison with the Jeryl Lynn-containing MMR vaccine (13–15), and 3) the clear net benefit of MMR immunization in a context of high incidence of natural mumps infection and a consequently high incidence of meningitis (16).

This study raises new practical questions regarding public health. The issue is not simply whether or not a specific vaccine is associated with an adverse event, but the extent to which a specific vaccination strategy influences the visibility of the adverse event despite its confirmed relative rarity, and hence affects public confidence. For example, the study by Reberrie and Galy-Eyraud (17) of MMR vaccine routinely administered to more than 3 million individuals in France found no excess risk of meningitis related to vaccine intake. This contrasts with the mass immunization campaign carried out in Brazil, where the high coverage rate achieved within a short time period meant that large numbers of individuals were exposed simultaneously, resulting in an observed cluster of meningitis cases. In Brazil, the target population of a mass immunization campaign typically includes hundreds of thousands of individuals. Furthermore, the features of the local medical care system also explain why aseptic meningitis outbreaks were observed mainly in large urban centers. In these cities, a great number of vaccinees live within the catchment areas of medical and public health surveillance services, which permits easier detection of any increase in the incidence rate of aseptic meningitis. Indeed, in Salvador, as well as in other

TABLE 2. Incidence and relative risk of aseptic meningitis before and after a mass immunization campaign with measles-mumps-rubella vaccine, by age, Salvador, Brazil, 1997

Age group (years)	Postcampaign*					Precampaign				
	No. of cases	Person-weeks of observation	Incidence rate ( $\times 10^{-6}$ )	Relative risk	95% confidence interval	No. of cases	Person-weeks of observation	Incidence rate ( $\times 10^{-6}$ )	Relative risk	95% confidence interval
1–3	15	462,312	3.24	3.09	1.20, 7.96	9	2,658,294	0.34	1.39	0.54, 3.60
4–8	37	788,160	4.69	4.47	1.89, 10.58	12	4,531,920	0.26	1.09	0.44, 2.66
9–11	6	570,904	1.05	1.00		8	3,282,698	0.24	1.00	

\* Cases with measles-mumps-rubella vaccination recorded.

urban centers in Brazil, including the capital cities where MMR mass immunization campaigns were carried out in the past, the majority of suspected cases of meningitis were transferred to a single referral hospital for infectious diseases. In Salvador, the number of children admitted to the referral hospital exceeded its capacity of 120 beds, which are usually filled with cases of other meningitis, sepsis, leptospirosis, tetanus, acquired immunodeficiency syndrome, and other infectious diseases. For almost 10 days in the 36th and 37th epidemiologic surveillance weeks, this unit was saturated with cases of aseptic meningitis.

Despite the absence of virologic confirmation, our results suggest a causal link between the MMR mass immunization campaign and the aseptic meningitis outbreak. Firstly, the outbreak curve clearly indicates a temporal association with the national vaccination day (figure 1). Secondly, elevated relative risks were estimated for the 36th–39th epidemiologic surveillance weeks in comparison with the precampaign period (table 1), corresponding to an increase in numbers of cases during the third to fifth weeks after vaccination and a return to normal levels thereafter (figure 2). Thirdly, similar outbreaks were observed in three other states where the MMR mass vaccination was also carried out, indicating a consistent association of aseptic meningitis with the MMR campaign (7). Therefore, it is reasonable to regard the Urabe mumps strain as the main risk factor associated with the aseptic meningitis outbreak following the mass immunization campaign in Salvador. Furthermore, a large relative risk was also identified using the case series method. However, in this context, the simpler comparison of pre- and post-campaign incidence rates was enough to provide a powerful and more direct quantification of the vaccine's effect, though it may have been prone to some bias due to misclassification of vaccine status in the underlying population.

A further finding is the different age distribution of MMR-associated aseptic meningitis. The target population of the Brazilian MMR mass immunization campaign was children aged 1–11 years, and this wide age range comprises older children generally not considered to be undergoing immunization for the first time.

Despite the high coverage rate for children of all ages in the mass immunization campaign, the risk of aseptic meningitis was heterogeneous by age. This finding raises two issues. Firstly, different coverage rates for different age groups might well have biased the estimation of the risk. However, as was noted above, vaccination uptake was similar across all age groups. Secondly, since everyone was exposed to MMR vaccine, the difference in incidence rates observed for the age groups suggests that the probab-

ity of contracting aseptic meningitis through exposure is age-dependent; this points to heterogeneity in the susceptibility to vaccine reactions during this mass immunization campaign. This finding could have been observed for two reasons: Firstly, susceptibility to MMR-associated adverse events itself is age-dependent, decreasing with increasing age. Secondly, it is reasonable to assume that only individuals previously noninfected with wild mumps virus are susceptible to such adverse events. Therefore, because the prevalence of antibodies increases with age (16, 18), the proportion of susceptible children (those never infected) is greater among the youngest children, and consequently the likelihood of vaccine reactions is higher in the same age range. Unfortunately, there is no up-to-date information on the prevalence of infection by age in Brazil, and we are not able to determine the actual age-specific risk of vaccine-associated aseptic meningitis.

The implications of the outbreak described in this investigation go beyond the medical care arena. Public confidence in mass immunization campaigns and the national immunization schedule is a concern of Brazilian public health officers. Reporting of adverse events could lead to a reduction in vaccination uptake, as occurred recently in the United Kingdom following the publication of an article suggesting a possible link between autism and MMR vaccine (19–21).

Indeed, such issues are not localized. Mass immunization campaigns have a central role in addressing vaccine-preventable diseases in Brazil. Despite some questions about the real advantages of mass immunization campaigns (22), this strategy has been widely used in Brazil because it has long been assumed to be the most cost-effective approach (23). However, despite the success of immunization campaigns, Brazilian society still faces the permanent menace of sudden outbreaks, which can also be triggered by any fall in vaccine coverage. São Paulo, the most populous city in the country, is a case in point: A recent measles outbreak there was attributed to a lower vaccination rate (24). Thus, it is necessary to maintain vaccination with very high coverage in Brazil.

The scenario is made even more complex by two important additional factors in Brazilian society today. Firstly, repeated cycles of mass immunization with high coverage rates over long periods of time have decreased the incidence of vaccine-preventable diseases. Such low incidence rates may change individuals' perceptions of the risk of infection by wild agents (25). Natural infection is no longer a living memory for many people, and their primary concern is now the safety of vaccines and misconceptions about the advantages of vaccination. Furthermore, natural infec-

tion and its outcomes might be seen by individuals as inevitable, whereas an adverse event caused by a vaccine might well be perceived as preventable, sufficient to stimulate refusals of vaccination. Secondly, there is increasing public demand for officials of health departments and immunization programs to detect and withdraw any unsafe products, as well as a demand for trustworthy information. The average citizen has started to behave as a health-care consumer, discussing official health policies, requesting more information, and questioning and even refusing governmental health measures. More and more health policies are being heavily influenced by public opinion. Problematic situations in health care have been reported by the media as scandals (26), and if the outbreaks described here attracted media attention in the cities where MMR mass immunization campaigns were carried out, it is because there is public demand for such information.

Until now, systemic factors related to health care delivery and insufficiency of information about the advantages of vaccination have accounted for the lack of proper immunization in Brazil and other developing countries (27, 28). However, with the ongoing changes described above, some public health officers argue that public belief in the beneficial end result of mass immunization campaigns is perhaps no longer enough by itself to prevent the increasing number of refusals of immunization. These factors are not exclusive to Brazilian society; they have been discussed elsewhere (29) in situations where decreases in vaccine uptake have followed publicity about adverse events. The Brazilian National Immunization Program has been very successful in promoting mass immunization campaigns with high coverage given the vertical and centralized structure of the program, which works countrywide. However, this positive experience has not been accompanied by improvements in the state Epidemiology Surveillance Services, which should also be responsible for monitoring adverse events. Furthermore, it is impossible to register data on individual vaccination status during a mass immunization campaign. This would permit future links with data on hospitalization or medical assistance, such as proposed surveillance for adverse events (30).

In this context, another important issue is how to convey information to the public. Managers of mass immunization campaigns in Brazil must consider the fact that despite much social change toward a more egalitarian society (31), the Brazilian population is very heterogeneous (32), with some of the most unequal income levels in the world. The diverse social stratification of the populace marks deep differences in levels of political engagement, schooling, and demands for civil rights. Currently, there is a consen-

sus among public health officers involved in the Brazilian National Immunization Program that in order to achieve their goal, it will be necessary to improve national and local surveillance for adverse events, as well as to promote appropriate dissemination of information to the public. It is unrealistic to consider providing detailed data—for instance, through extensive vaccine information pamphlets—or even to require written consent before each shot given during a mass immunization campaign (33). On the other hand, it is necessary and feasible that parents have the opportunity to ask questions at the vaccination site, to receive appropriate recommendations and information on adverse events, and to gain access to educational material, and that field-workers involved in a mass immunization campaign be able to provide reliable information, especially on the many advantages of vaccination (22).

The evaluation of adverse events following vaccination during immunization campaigns has been carried out in the past, as well as recently in studies of Guillain-Barré syndrome associated with the use of influenza vaccine (34) and measles vaccine (35). Our experience has demonstrated again that mass immunization campaigns can provide a unique opportunity to explore possible associations between vaccination and rare adverse events. During mass immunization campaigns, a great number of individuals are vaccinated in a short period of time. Therefore, even rare adverse events can readily be detected, and a causal link can be established using appropriate methods.

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