Mumps caused by an inadequately attenuated measles, mumps and rubella vaccine

WJ Bakker MD MPH[1], RG Mathias MD[2]

WJ Bakker, RG Mathias. Mumps caused by an inadequately attenuated measles, mumps and rubella vaccine. Can J Infect Dis 2001;12(3):144-148.

PROBLEM: Reports of mumps following measles, mumps and rubella (MMR) immunization.
OBJECTIVE: To determine whether mumps was caused by immunization or whether there was a concurrent epidemic of a wild strain of mumps.
DESIGN AND PARTICIPANTS: Analysis of surveillance data and a cohort study of three schools that participated in the campaign.
OUTCOME MEASURES: Cases of clinical mumps and orchitis, and immunization history and records were reviewed. The MMR vaccine was produced by the Serum Institute of India and contained the Leningrad-Zagreb strain of mumps virus. Four lots were used in the specific immunization campaign.
RESULTS: Sentinel health facility surveillance showed an increase in mumps after two school immunization campaigns in western Suriname and a mass immunization campaign in the same region. There was also an increase in a geographically separate region following a mass campaign with the same vaccine. Three hundred fifteen children from three schools that were targeted in the immunization campaign were interviewed. The attack rate for mumps in those immunized was 15.1%; in those not immunized, the attack rate was 4.7%. In the affected males, the attack rate for orchitis was five of 19 (21%). Assuming 90% protection by the MMR vaccine, the incidence ratio (observed to expected) was 32.
CONCLUSIONS: The mumps outbreak was caused by an inadequately attenuated MMR vaccine. Because this vaccine had not been used in these populations before in Suriname, it was not possible to determine wether the outbreak was due the virulence of the Leningrad-Zagreb mumps strain or due to production problems with one or more specific lots of vaccine. The vaccine was withdrawn from further use.

Key Words: *Attenuation; Infection; Mumps; Outbreak; Vaccine; Vaccine failure*

Oreillons causés par un vaccin ROR mal atténué

PROBLÈME : Rapports sur des cas d'oreillons après une immunisation contre la rougeole, les oreillons et la rubéole (ROR).
OBJECTIF : Déterminer si les oreillons ont été causés par l'immunisation ou par la présence concomitante d'une épidémie d'oreillons de souche sauvage.
MODÈLES ET PARTICIPANTS : Analyse des données de surveillance et étude de cohortes provenant de trois écoles qui ont participé à la campagne de vaccination.
MESURES PARAMÉTRIQUES : Les cas d'oreillons et d'orchite clinique et les antécédents des dossiers d'immunisation ont été passés en revue. Le vaccin ROR a été fabriqué par le *Serum Institute of India* et renfermait la souche Leningrad-Zagreb du virus des oreillons. Quatre lots ont spécifiquement été utilisés dans cette campagne.
RÉSULTATS : La surveillance effectuée par l'établissement de santé sentinelle a fait état d'une augmentation des cas d'oreillons après deux campagnes d'immunisation scolaire dans la partie occidentale du Surinam et après une campagne d'immunisation de masse dans la même région. On a en outre noté une augmentation dans une autre région après une campagne d'immunisation de masse au moyen du même vaccin. Trois-cent-quinze enfants provenant de trois écoles qui étaient ciblées par la campagne d'immunisation ont été interrogés. Le taux d'oreillons chez les sujets immunisés a été de 15,1 %; chez les

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[1]*Bureau of Public Health, Ministry of Health, Paramaribo, Suriname;* [2]*Pan American Health Organization/World Health Organization, Paramaribo, Suriname*
Correspondence and reprints: Dr RG Mathias, Health Care and Epidemiology, University of British Columbia, 5804 Fairview Avenue, Vancouver, British Columbia V6T 1Z3. Telephone 604-822-2772, fax 604-822-4994, e-mail mathias@interchange.ubc.ca
Received for publication November 26, 1999. Accepted June 23, 2000

sujets non immunisés, il a été de 4,7 %. Chez les garçons affectés, le taux d'orchite a été de 5/19 (21 %). En supposant une protection de l'ordre de 90 % pour le vaccin ROR, le ratio d'incidence (observé ou prévisible) a été évalué à 32. **CONCLUSION :** L'éclosion de cas d'oreillons a été causée par un vaccin ROR mal atténué. Parce que ce vaccin n'avait pas été utilisé auparavant chez ces populations du Surinam, il a été impossible de déterminer si l'éclosion a été attribuable à la virulence de la souche d'un virus Leningrad-Zagreb ou à des problèmes de fabrication de l'un ou plus des lots de vaccin. Le vaccin a été retiré du marché.

Following an immunization campaign of school children in Suriname, mumps was diagnosed by community physicians. They noted that the cases that they were seeing were postimmunization and requested public health authorities to investigate.

The routine immunization program for measles, mumps and rubella (MMR) immunization in Suriname takes place at public preschool clinics. Most immunization has been completed by the age of two years. The school immunization program usually consists of a rubella vaccine given on entry to school and a catch-up program in grade 6. In 1998, because of a rubella outbreak and subsequent control measures, rubella vaccine was in short supply, prompting immunization authorities to initiate an MMR vaccine program to immunize grades 1, 3 and 5 for 1998 and 1999, thus improving coverage for all three diseases in schools. The western section of Suriname, Nickerie, initiated this program the week of June 8, 1998 in four schools for two weeks; it continued the week of July 16, 1998 in two other schools and returned to a third school that had not finished the June program. This program comprised the six schools of the region.

A mass rubella immunization campaign for coastal Suriname was planned because of an outbreak of rubella earlier in 1998. People aged five to 39 years were targeted. Because of the shortage of rubella vaccine, it was decided that the MMR vaccine would be used. This program was initiated first in a district just outside of the capital of Suriname, Paramaribo. Because of the mumps outbreak, a mass immunization campaign against mumps was initiated to control the mumps outbreak in the Nickerie region in early August 1998; the MMR vaccines were of the same lots that were used in the previously scheduled school immunization program. Approximately 16,600 people aged five to 39 years were immunized over the three-week period. Again, an increase in mumps cases was reported two to three weeks after this campaign. The MMR campaign was terminated when the increase in mumps cases was again noted.

Mumps is reported via the sentinel health clinic reporting system in Suriname. Selected physicians representing both private and public clinics are phoned weekly for reports on a variety of diseases, including mumps.

The vaccine used in the 1998 school program and the mass campaigns was MMR vaccine produced by the Serum Institute of India Ltd. Four lot numbers were used – 186, 202, 212 and 225; about 75% of the vaccines were lot number 202 (1). Specific lot numbers were not recorded on the immunization record. The mumps strain in the vaccine was the Leningrad-Zagreb strain. The vaccine was handled by the Expanded Program on Immunization cold chain guidelines (2). No vaccine handling problems were noted.

INVESTIGATION

July and August 1998: Of 29 cases of mumps reported during the week of June 30 to July 4, 1998 to the sentinel physician reporting system (expected number of cases was two), 26 were from the subsequent investigation area. Of these 26 cases, 24 had received the MMR vaccine two to three weeks before the onset of mumps. Six further cases were found during a case finding study. Children at six schools had been immunized with MMR as part of the planned routine immunization campaign for grades 1, 3 and 5. These grades had been immunized during the weeks of June 8 and 15, 1998, and on July 16 and 17, 1998.

September 1998: In September 1998, a further case investigation was carried out. A total of 321 mumps cases were reported by physicians in the western area of Suriname via the sentinel system, but there were no identifiers or epidemiological details reported, such as age and sex. Physicians again confirmed their impression that the mumps cases followed immunization with MMR vaccine. A line listing with identifiers and epidemiological information was developed in preparation for a vaccine evaluation study.

October 1998: In October 1998, a cohort study of the grades immunized in the school campaign was organized and carried out in three schools. The schools were sampled using a convenience sample chosen by school size. The team knew that all schools had reported mumps in the period covered by the study.

In one school, the immunization records were available. The study recorded the child's immunization status or date of immunization, along with illness compatible with mumps, defined as salivary gland swelling with fever. Identifiers of name, address, date of birth and sex were also recorded. Children who were absent on the immunization days in June 1998 visited the regional clinic for immunization. The school records may not have accompanied the child and, hence, may not have been completed. Immunization status was taken from the immunization book, when available, or the child's recollection of immunization. Complications such as orchitis were asked about in the personal interview and confirmed from the public clinic records. All data were entered into an Excel (Microsoft Corporation, USA) spreadsheet file for analysis.

RESULTS

Sentinel surveillance system results: The mumps reports from the sentinal surveillance system are presented in Figure 1. Reporting weeks 22 to 40 for the years 1997 and 1998 are shown. There were no reported cases of mumps in Nickerie in 1997. There was a low, varying number of cases of mumps for the rest of Suriname. In the same period in 1998, Nickerie

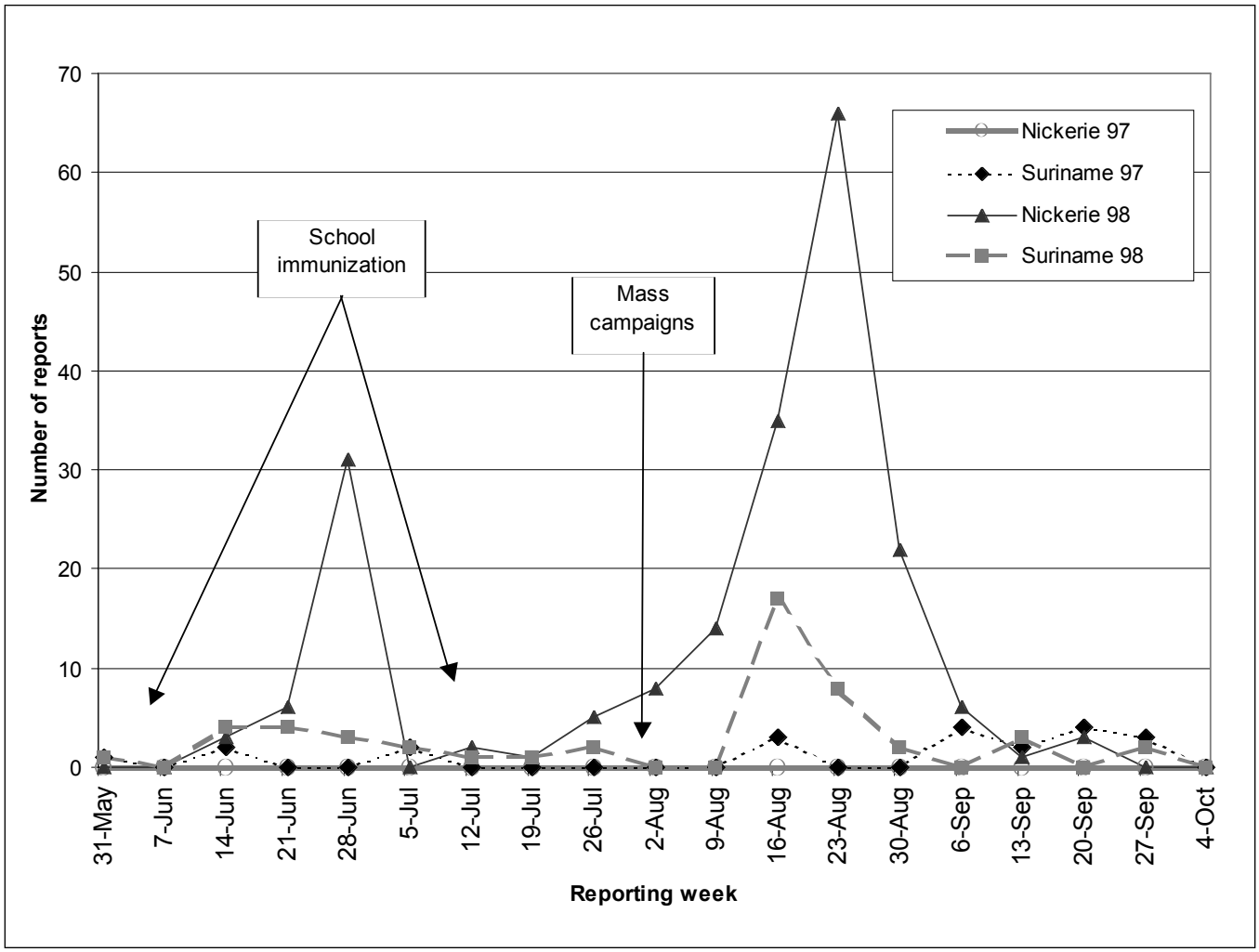

Figure 1) *Cases of mumps as reported to the sentinel surveillance system, 1997 to 1998. Reporting weeks 22 to 40 are shown*

TABLE 1
Distribution of children interviewed in Suriname, by school

	Males		Females		
School	n	Average age (years)	n	Average age (years)	Total (n)
1	79	9.9	62	10.2	141
2	41	9.8	35	10.4	76
3	41	9.6	57	10.7	98
Total	161	9.8	154	10.4	315

TABLE 2
Immunization rates for mumps, measles and rubella (MMR) in Suriname, by school

	MMR vaccine given			
School	Yes (n)	No (n)	Total (n)	Immunization rate
1	117	24	141	83%
2	69	7	76	91%
3	86	12	98	88%
Total	272	43	315	86%

showed a marked increase in cases with two major peaks between June 21 and 28, 1998, and then again between August 6 and September 9, 1998. During this latter period, there was also a peak in the rest of Suriname for the weeks of August 16 and 23, 1998. The cases in the rest of Suriname were from the district just outside of the capital, Paramaribo, where the mass rubella immunization campaign had begun the week of August 2, 1998 and had continued through the week of August 16, 1998. In Nickerie, the mass campaign had started at about the same time and had continued through the week of August 16, 1998.

Cohort study results: Three hundred fifteen children were interviewed of the 329 enrolled children. The remaining 14 students were absent on the day that the team visited. The total school population in this area is about 497 children. Thus, 63% of children in the affected area who were in the grades included in the program were part of the study. The present analysis is restricted to the 315 children who were interviewed by the study team.

School 1 is the largest of the schools included in the study. The three schools in which students were not interviewed were about the size of school 3 or smaller. The average ages

TABLE 3
Attack rate of mumps in Suriname in 1998, by age group

	Mumps			
Age range	Yes (n)	No (n)	Total (n)	Mumps attack rate
9 years or younger	14	99	113	12%
10 to 11.9 years	15	109	124	12%
12 years or older	14	64	78	18%
Total	43	272	315	14%

TABLE 4
Attack rate of mumps in Suriname in 1998, by MMR immunization status

	MMR vaccine given			Immunization
Mumps	Yes	No	Total	rate
Yes	41	2	43	95.3%
No	231	41	272	84.9%
Total	272	43	315	86.3%
Attack rate for mumps	15.1%	4.7%		

MMR Measles, mumps and rubella

were similar in all three schools. The females from school 3 were slightly older (Table 1).

The immunization rates for boys and girls were similar at 85% and 87%, respectively. The immunization rates by school (Table 2) showed that school 1 had lower rates of immunization.

The immunization rates for schools 2 and 3 are similar. As noted above, these rates were derived mainly from the children's recollection. The rate for school 1 was derived from the child's recollection and the immunization record. Some children were immunized subsequently at the clinic, but these results were not necessarily recorded on the child's immunization record. According to the memory of the nurse and the school principal, the immunization rate may have been as high as 98% of the children still in the school. Further analysis used the lower rate, recognizing that there was some misclassification but that it was similar for all three schools and allows some comparison to be made.

There was also difficulty in determining the relationship of the MMR immunization and the onset of mumps due to the mass campaign carried out in August 1998. Children were eligible for both programs. Many of the children who presented with mumps were also reimmunized with MMR vaccine when they presented as cases. This occurred because there was concern that if the children were not protected from mumps, they may have received inactivated vaccine and needed to receive the MR component of the vaccine again. It was very difficult to sort out these possibilities by history, two to three months postimmunization. Time of onset of cases was taken from the initial case study and the regular surveillance data of the region.

Mumps attack rates were 16% in boys and 12% in girls. This difference in attack rates was confirmed by the regional clinic records.

The attack rate for mumps was higher in school 1 at 16%. If the mumps cases were associated with immunization, then this observation may support the higher estimated rate for immunization in this school. The rates of mumps in the other two schools, 12% and 11%, were also higher than expected, but the differences were not significant. The attack rate for mumps was higher in the oldest age group.

The vaccine efficacy is –224% calculated by the formula (1):

$$\frac{\text{(attack rate unimmunized – attack rate immunized)}}{\text{attack rate unimmunized}}$$

The Fisher's exact two-sided test for this distribution is P=0.06. The relative risk (unimmunized/immunized) is 3.2. However, this assumes that the expected distributions are the same (the null hypothesis); in the present case, the expected distribution is that the number of illnesses in those who are immunized should be much less than in those not immunized, rather than the reverse. With the expectation that the attack rate in the immunized should be 10% of the rate in the unimmunized – that is, 4.7/1000 rather than 151/1000 – the incidence ratio (observed/expected) is 32 with 95% confidence limits of 37 to 27.

In each of the schools, children in grades 2, 4 and 6 were questioned about the occurrence of mumps. In school 2, no children in those grades had mumps. In school 1, five children in those grades had mumps – four after receiving the MMR vaccine and one some weeks before. In school 3, five children had mumps, all in grade 4. They all reported mumps following immunization in the mass campaign of early August 1998.

During 11 home visits to clarify the diagnosis or immunization status, or to obtain data on an absent child, there was only one family in which there may have been transmission of mumps. This was not an outbreak-related case, because the mumps occurred in April 1998 – well before the outbreak was investigated – in the child and was apparently transmitted to the mother.

Complications of mumps were reported in the boys, with an orchitis rate of five of 19 (21%); the orchitis status unknown in two cases. In girls, four of eight (50%) had lower abdominal pain associated with the mumps, and status was unknown in nine cases. No case of possible mumps aseptic meningitis was seen at the public clinic or was admitted to hospital during this period.

DISCUSSION

Mumps is clinically diagnosed in most cases. The characteristic salivary gland swelling, particularly when associated with orchitis in boys, is a specific diagnosis in an outbreak situation. The rate of orchitis cases increases with age (3). In this outbreak, the clinical diagnosis was made by several physicians. The presence of orchitis makes it very unlikely that the syndrome reported was anything other than mumps.

In community outbreaks of measles, particularly in a highly immunized population, the majority of cases occur in

the immunized population, even though the rate of cases is higher in the unimmunized (4). Also, in a community outbreak of a communicable disease, the cases occur in waves proportional to the incubation period of the agent (5). The usual incubation period of mumps is 12 to 25 days, with a mean of 18 days (1). There was no increase in the number of cases in this region until after the immunization program, and it faded quickly after the program. This is not the expected pattern of a natural mumps infection.

In the present outbreak, the rate of mumps cases was higher in the immunized than in the unimmunized group by a relative risk greater than 3. Mumps vaccine in clinical trials has had a vaccine efficacy of 95% (6,7), and in field trials, it varies but still has a vaccine efficacy of 90% or more (8,9). Using this to calculate the expected number of cases, the incidence ratio calculated from the observed/expected ratio is about 32 with confidence limits of 27 to 37 using a Poisson distribution.

Because previous school campaigns had used the rubella vaccine only, this is the first campaign in Suriname to use the MMR vaccine in people over the age of five years. Odisseev and Gacheva (10) have described mumps vaccine-associated meningitis following immunization in the four- to 12-year-old age group in Bulgaria, resulting in withdrawal of the vaccine. Consideration of the safety and efficacy of mumps vaccine lead Noles and Anderson (11) to conclude that, for higher efficacy, greater reactogenicity could be tolerated when comparing the Jeryl-Lynne strain with the Urabe strain of vaccine. This was disputed by Nalin (12), who felt that the public concern was not well considered and that there was an advantage to using an efficacious but safer mumps vaccine. Certainly the professionals and public associated with the immunization campaign were concerned about mumps caused by the vaccine, even though meningitis had not been diagnosed. Wild strain mumps causes complications, which is the reason for an immunization program. If the vaccine can cause complications at a level near to the same level as the wild strain virus, then the rationale for immunization is not valid. We did not detect any encephalitis, but the rate of encephalitis after mumps is about 1/1000 (13). With the difficulties in the attenuation of the mumps virus (14), it may not be surprising that some strains are less attenuated than others. Nevertheless, the rate of clinical mumps and the associated complication of orchitis were such that the vaccine was withdrawn because of concerns that more serious complications or death may occur with its continued use.

The findings of this outbreak are compatible with those of an outbreak of mumps caused by the mumps vaccine. Mumps would not be expected to be seen following the immunization of infants, because most cases of wild mumps are subclinical in the under two years age group. Also, routine MMR vaccination programs in early childhood do not immunize as many children in as short a time period as this specific school-aged catch-up program. Thus, surveillance programs would probably not detect a relatively low rate of mumps from these lots of vaccine. Nevertheless, the infections of the central nervous system may occur even in the young age groups (13).

RECOMMENDATION

The available evidence supports that this outbreak was vaccine associated. Whether the vaccine virus was insufficiently attenuated or not attenuated at all cannot be answered by this investigation. Nevertheless, the investigating team recommended that the implicated lots of vaccine be withdrawn from further use in all age groups over two years and that, as soon as possible, all vaccine from these lot numbers (202, 212 and 225) be replaced with a more attenuated form of mumps vaccine. Because this is the first use of MMR vaccine in older individuals in Suriname, it is recommended that a different strain of mumps virus strain be used in the replacement vaccine until the attenuation of this strain can be fully evaluated.

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