The increased use of mumps vaccine worldwide has reduced the incidence of complications associated with mumps caused by wild virus, including aseptic meningitis, which occurs in up to 10% of people with wild-virus mumps. However, as wild-virus mumps circulation has declined and mumps vaccine use has increased, adverse events associated with the mumps vaccine have come under increasing public and scientific scrutiny.

Moreover, intensified efforts towards measles elimination and rubella control has led to recent expanded use of mumps vaccine in developing countries, particularly in the Americas: a key strategy for measles elimination is mass vaccination campaigns, with measles vaccine frequently administered as a combination vaccine including rubella and mumps vaccine strains.

In May 2001, recommendations for mumps vaccine use were discussed by an expert committee at the World Health Organization (WHO), Geneva. Participants reviewed data on reactogenicity of mumps vaccine strains, as well as available information on immunogenicity, efficacy, cost, and supply. Mumps circulation has declined and mumps vaccine use has increased, adverse events associated with the mumps vaccine have come under increasing public and scientific scrutiny.
vaccine virus strains have been associated with aseptic meningitis, with widely varying estimates of risk.\textsuperscript{1–7} These discrepancies in estimated rates may be due to differences in study design or case ascertainment as well as in vaccine strains.\textsuperscript{3,8} Therefore, the meeting recommendations highlighted the need for enhanced efforts to determine the rate of adverse events following immunization associated with different preparations of mumps vaccine.\textsuperscript{6} Although a number of studies are available on the risk associated with other strains, limited data are available on the risk of aseptic meningitis associated with the Leningrad-Zagreb (L-Z) strains of mumps vaccine.\textsuperscript{1,9–13} In this study we estimate the risk of aseptic meningitis associated with administration of L-Z vaccine during a mass campaign targeted to more than 100,000 children in the state of Rio Grande do Sul, Brazil. In addition, we demonstrate the impact of the mass vaccination campaign on the incidence of wild-virus mumps in the 3-year period following the campaign.

### Methods

The mumps-measles-rubella (MMR) vaccine was produced by Serum Institute of India, Lot: 180-X: Measles: Edmonston-Zagreb; Mumps: Leningrad-Zagreb; Rubella: Wistar RA 27/3. Vaccine lots met the requirements of the national regulatory authority, including quality control standards for potency, toxicity and safety.

#### Vaccination campaign

A measles outbreak in 1997\textsuperscript{5} provided the impetus for a mass vaccination campaign with MMR, which served to introduce mumps and rubella vaccines among children aged 1–11 years. Five contiguous, primarily urban municipalities with a target population of 110,629 children aged 1–11 years had exclusive distribution of L-Z vaccine. The campaign was conducted between 8 September and 28 November 1997 (weeks 37–48).

#### Mumps surveillance

Mumps surveillance has been conducted in Rio Grande do Sul since 1984. It is a passive system which depends on notification by health care providers to the municipal health services. Aggregate numbers of cases of mumps by month of onset and age group are reported monthly from the municipal to the state level. Vaccination status of mumps cases has not been routinely collected as part of disease surveillance, as mumps vaccination was only introduced in 1997. Mumps cases are diagnosed clinically, and are generally recognized as acute onset of unilateral or bilateral tender swelling of the parotid or salivary glands lasting \(\geq 2\) days without other apparent cause.

#### Meningitis surveillance

Meningitis surveillance is conducted through a passive surveillance system. Cases are reported by clinicians to the municipal epidemiological services, whose staff perform the case investigation. The national case investigation form was introduced in January 1995. As part of routine investigation, municipal health workers use this form to collect clinical and laboratory data. The MMR vaccination history, including date of vaccination, is also collected on this form. Thus, case ascertainment is independent of vaccination history.

Verification of MMR receipt during the campaign was based on verbal history obtained from parents or guardians or on written information from vaccination cards. We consider the verbal information on date of vaccination highly reliable because the case investigation was conducted during the acute phase of the child’s illness and also within a short period after the campaign. Furthermore, mass vaccination campaigns are marked with extensive events easily recalled by parents. Children aged 1–11 years would not have been eligible for any injectable vaccine during the campaign other than MMR. Thus, we consider it very unlikely that children or parents would have falsely reported being vaccinated when they were not, minimizing ascertainment bias with possible overestimation of vaccine risk.

#### Case definition

A case of aseptic meningitis from any cause was defined as occurrence of clinically diagnosed meningitis in a person with a cerebrospinal fluid (CSF) pleocytosis (between 5 and 1500 leukocytes/ml) and a negative gram stain. Viral isolation is not routinely performed in Rio Grande do Sul. Mumps-associated aseptic meningitis was defined as that occurring in conjunction with or following clinically diagnosed mumps. For purposes of this study, a case of vaccine-associated aseptic meningitis was defined as aseptic meningitis with a pleocytosis of 10–1500 leukocytes/ml and occurring within 15–35 days after vaccine receipt. We used a lower limit of 15 days to avoid classifying cases of febrile convulsions following measles vaccination as vaccine-associated aseptic meningitis, and to facilitate risk comparisons with other similar studies.\textsuperscript{3,14}

#### Risk analysis

To estimate the increased overall risk of aseptic meningitis (all-cause) associated with the mass campaign, we compared the incidence of aseptic meningitis among children aged 1–11 years in the period during the campaign in 1997 with the average incidence of aseptic meningitis during the same period and in the same age group in 1995–1996. We used a 2-year period to allow for a more stable baseline rate. Because MMR was not used prior to its introduction in the campaign of 1997, the populations in the five municipalities in 1995–1996 were considered unexposed to MMR. Although some doses may have been available previously through the private sector, vaccinations received in the private sector generally represent a negligible fraction of doses administered. Vaccines are provided free of charge in the public sector, and are paid for out-of-pocket in the private sector.

Because all vaccine-associated cases in 1997 occurred between September 23 and November 20 (weeks 39 and 47), we used the same 9-week period to estimate baseline risk during 1995–1996. The denominator of person-weeks during baseline and exposure periods was estimated by using 9/52 of the population of children aged 1–11 based on national census data. The 1996 national census data available from the Brazilian Institute of Geography and Statistics included estimates for the population 1995–1997. The risk of aseptic meningitis was expressed as the number of cases per 10,000 person-weeks at risk.
To estimate the reactogenicity of the L-Z vaccine strain, we included only those cases of aseptic meningitis that met the definition of a vaccine-associated case. The risk of vaccine-associated meningitis was then estimated using as a denominator the number of doses administered and was expressed as the ratio of cases: 10,000 doses applied.

To estimate the impact of the mass vaccination campaign on overall mumps incidence, we calculated age-specific mumps incidence for the pre-campaign period, 1984–1996, and the post-campaign period, 1998–2000, using the following age groups: <1, 1–14, and ≥15 years. These age groups were used to estimate the direct and indirect impact for the groups targeted and outside of the target age groups for vaccination. Children aged 11, 12, and 13 years were included within the target age group for the period 1998–2000 to account for ageing through the birth cohort (i.e. children targeted by the campaign in 1997 who then aged into the older cohorts). For denominators, we used the midpoint population estimate within each age group.

EPIINFO Version 6 was used for the calculations of relative risk, using the Fleiss approximation to calculate 95% CI.

**Results**

A total of 105,098 doses of L-Z were administered to children aged 1–11 years, for an overall coverage of 95%. Coverage in the remainder of the region was 93% (62,296 doses administered). In the study area, from 23 September to 20 November, 55 cases of aseptic meningitis (all causes) were reported among children aged 1–11 years (Figure 1). The peak of the epidemic was in week 41 (third week following the start of the campaign), with 16 cases. Although we do not have data on vaccination coverage by week, this curve parallels the pattern of vaccination during campaigns lasting longer than one month in Brazil, with the highest demand for vaccination in the early weeks of the campaign. The cost and effort of social mobilization generally require focusing publicity in the first 2–3 weeks of the campaign.

The rate of aseptic meningitis during the 9-week period of 1997 was 28.7 cases/10,000 person-weeks. During the same periods in 1995–1996, an average of 4.5 cases of aseptic meningitis were reported, for a rate of 2.4 cases per 10,000 person-weeks. Thus, the risk of aseptic meningitis following the campaign was increased 12.2-fold (95% CI: 6.0–24.7) compared with the same period in 1995–1996.

Of the 55 cases of aseptic meningitis, 45 had a history of vaccination with MMR, however, only 31 were classified as vaccine-associated based on our case definition. Among vaccine-associated cases, 18 (58%) were male, and the median interval between vaccination and onset of symptoms was 19 days (range 15–33). The median number of leukocytes was 474. The median age was 6 years. The risk of vaccine-associated aseptic meningitis was 2.9 cases per 10,000 doses of L-Z administered (equivalent to 1 case per 3390 doses administered). Within the 1–11 age group the risk did not differ significantly by age group (data not shown).

The impact of the campaign on mumps and wild-virus-associated mumps aseptic meningitis was substantial in these five municipalities. In the 3-year period from January 1998 through December 2000 no cases of aseptic meningitis (mumps-associated) were reported among children aged 1–11 years. In contrast, in the approximately 2.5 years from January 1995 through August 1997, 16 cases of mumps-associated aseptic meningitis were reported in the same age group.

The overall annual average rate of mumps from 1984 to 1996 was 115/100,000 (median 129, range 23–278), whereas in

![Diagram](https://academic.oup.com/ije/article-abstract/31/5/978/745807)
the 3 years following the campaign, the rates were 10, 8, and 6 cases per 100,000 in 1998, 1999, and 2000, respectively, for an overall decline of 93% (Table 1).

The incidence declined rapidly both within and outside of the age group targeted by the mass vaccination campaign: among children aged <1 year, mumps incidence declined by 92% (83 to 7 per 100,000) and among those aged ≥15 years, mumps incidence declined 93% (43 to 3 per 100,000) (Table 1).

Discussion

We observed an increased incidence of aseptic meningitis following mass vaccination with MMR containing the L-Z mumps strain, with an estimated risk of 2.9 cases per 10,000 doses (equivalent to 1 case to 3390 doses). We believe this represents a conservative estimate, because we used a specific case definition to avoid classifying cases of febrile convulsions following MMR vaccination as vaccine-associated aseptic meningitis as vaccine-associated aseptic meningitis.3, 14 These findings suggest L-Z is more reactogenic than Urabe and Jerry-Lynn strains. 3, 15 However, the scarcity of published data limits comparison with these or other estimates. The estimate of 9 cases of aseptic meningitis per 10,000 doses from Zagreb, Croatia was based on passive record review in a period when MMR was administered as part of a routine programme (rather than mass vaccination).9 Kraigher, in a personal communication,1 reported a risk of 0.2 cases per 10,000 doses. Beck12 reported distribution of 10 million doses of L-Z in Yugoslavia and elsewhere with rare reports of aseptic meningitis. However, the vaccination strategy and the case ascertainment methods are not reported. In a post-licensure clinical trial of various preparations of MMR vaccines, Ranier et al.10 found a sixfold increased risk of mumps parotitis for MMR containing L-Z strains (4.4% of 2226) compared with those containing the Jeryl-Lynn strains (0.7% of 2216), and a threefold increased risk compared with MMR containing Urabe strains (2.8% of 2179). The sample size was not sufficient to estimate rare events such as aseptic meningitis. A recent report from Surinam estimated a mumps incidence of 15% following mass vaccination with L-Z; no cases of aseptic meningitis were reported.13 Because we had no virus isolates from cases of aseptic meningitis in this study, we cannot definitively exclude the possibility that other circulating viruses may have caused the observed epidemiic patterns. Nonetheless, the possibility that this outbreak was caused by another virus, such as an enterovirus or even indigenous mumps virus, is remote. The epidemic curve is consistent with a common source outbreak: that is, simultaneous exposure of a group of people to a single aetiological agent characterized by a sudden increase with no secondary cases.16 Had another virus been circulating, we might have expected an increase in secondary cases of meningitis, including cases outside the age group targeted by the vaccine. No secondary cases were identified within families, and we observed no increase in other age groups outside of the target age group (data not shown).

This mass campaign with MMR provided an opportunity to estimate risks for an adverse event that would normally have gone undetected. Passive adverse events surveillance systems are subject to underreporting, especially for less severe events with no sequelae such as vaccine-associated aseptic meningitis. In the UK, an increase in cases of aseptic meningitis was not detected through the passive adverse events surveillance system. Subsequent investigation identified an increased risk of aseptic meningitis associated with receipt of Urabe among children aged 1–2 years.3 In Rio Grande do Sul, the cluster of cases coincident with mass vaccination led to media attention which in turn likely increased the sensitivity of the surveillance system through increased awareness of parents and health care providers. A similar situation occurred in Japan in 1991.2 Due in part to increased publicity, children with aseptic meningitis were brought to the attention of the health care system when otherwise they might usually have stayed home because of the relatively moderate signs and symptoms. Evaluation of these cases by CSF analysis identified a large number of cases that otherwise would have remained undetected.2

The MMR mass vaccination campaign had a dramatic immediate impact on mumps and aseptic meningitis associated with wild virus mumps, both in age groups targeted and outside of those targeted by the campaign. Mass vaccination in combination with high routine coverage has been a critical component of the measles elimination strategy for the Americas.4 As of September 2001, all but four countries in the Americas (Haiti, Dominican Republic, Paraguay, and Peru) were using measles vaccines combined with mumps and rubella vaccines in their routine childhood vaccination schedule (Carlos Castillo-Solorzano, WHO/Pan American Health Organization, personal communication) as well as for mass vaccination. Use of mumps in these campaigns provides an opportunity for a second dose of mumps with little additional programme cost.

Table 1 The impact of mass vaccination with Leningrad-Zagreb mumps vaccine strain on mumps disease in five selected municipalities, Rio Grande do Sul, Brazil, 1984–1996 and 1998–2000

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Total cases</td>
<td>Annual average cases</td>
</tr>
<tr>
<td>&lt;1</td>
<td>97</td>
<td>7.3</td>
</tr>
<tr>
<td>1–14</td>
<td>4794</td>
<td>369</td>
</tr>
<tr>
<td>15+</td>
<td>1862</td>
<td>143</td>
</tr>
<tr>
<td>Total</td>
<td>6733</td>
<td>519</td>
</tr>
</tbody>
</table>

a Column 2/13 years.
b Rate by 10^5 population in the age group in the mid-point period of 1984–1996 (1990).
c Column 5/3 years.
d Rate per 10^5 population in the age group in the mid-point period of 1998–2000 (1999).
e [(column 4 – column 7)/column 4] × 100.
However, the advantage of the immediate impact of mass vaccination with mumps vaccine must be weighed against the increased visibility of adverse events in the population. Although vaccine-associated aseptic meningitis is infrequent, generally of short duration and without sequelae, a low risk occurring within a short time period can lead to crowded hospital wards and possible loss of public confidence in the vaccine programme. Depending upon the public threshold for tolerance of adverse events, even a low risk detected as part of a routine vaccination programme can lead to withdrawal of the product from the market. Such is the case in Japan, where MMR containing the Urabe mumps strain was used from 1989 to 1993 and then withdrawn from the market because of concerns about aseptic meningitis.

Mumps immunization strategies have implications for mumps-containing vaccine supply and demand. If mumps control or elimination is ‘piggybacked’ onto measles elimination and rubella control, with increased use of MMR in mass campaigns, demand for MMR will also increase. Thus, cost and availability will become more important factors in determining type of vaccine used, particularly in countries where financial resources for the public health sector are limited. The currently available MMR vaccines have been offered for purchase to the countries of the Americas at the following prices: Jeryl Lynn, US$1.50/dose; Urabe: 0.7955/dose. In 1997, L-Z was offered for purchase to the countries of the Americas at US$0.49/dose. Because of its low price and availability, L-Z may play an important future role in supplying the future demand for MMR vaccines worldwide.

Each country must weigh the public acceptability of the known rate of adverse events and their potential impact on the overall programme along with other available data on vaccine safety, immunogenicity, efficacy and cost to determine vaccines used for routine and mass immunization. The WHO has recommended enhanced efforts to determine the rate of adverse events following immunization associated with different mumps vaccine preparations. We have presented here additional data for decision making in national vaccination programmes.

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KEY MESSAGES

- The risk of vaccine-associated aseptic meningitis following a mass campaign with mumps-measles-rubella (MMR) vaccine using the Leningrad-Zagreb (L-Z) strain of mumps vaccine was estimated at 1 case per 3390 doses administered.
- The use of this vaccine strain as part of a campaign strategy facilitated detection of events that might have gone undetected with routine use of the same vaccine.
- In the 3-year period following the campaign, the incidence of mumps declined 93%.
- Country-specific decisions about vaccine strains used for routine and mass vaccination should consider vaccine safety issues and public confidence in the vaccine programme as well as cost, availability, and vaccine efficacy.

References