Safety Evaluation of MMR Vaccine during a Primary School Campaign in Saudi Arabia

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Summary
Monitoring of adverse events following the administration of MMR vaccine containing the Urabe mumps virus vaccine strain, to over 2 million schoolchildren (aged 6–13 years) revealed that the incidence of vaccine-associated aseptic meningitis was one case per 295 000 doses given. About 92 per cent of these children had had their primary immunization against MMR at 12 months of age and, therefore, were probably not immunologically naïve. It appears from our data that the use of the Urabe-based mumps vaccine in the booster-dose format induces much less adverse effects than usually observed following the primary immunization with it. Further studies are needed to prove this conclusively.

Introduction
MMR vaccine was introduced in the Saudi Expanded Programme of Immunization (EPI) in 1991. Since then, the vaccine has been given compulsorily to all children around the age of 12 months. MMR vaccine used in Saudi Arabia during the current campaign contains Schwartz strain live attenuated measles virus, Urabe strain live attenuated mumps virus and RA27/3 live attenuated rubella virus. Within EPI, MMR vaccination coverage in the Kingdom of Saudi Arabia reached 88 per cent in 1992 and since then, more than 90 per cent coverage has been maintained annually.1 In 1991 a two-dose policy of measles vaccination was integrated into the EPI at the ages of 6 and 12 months, the second dose being MMR. The impact of this policy and the maintenance of high vaccination coverage are reflected in the epidemiological pattern of measles in Saudi Arabia. The percentage of cases among children over 15 years increased from 10 per cent in 1987 to more than 40 per cent in 1997, while the percentage of cases among 1–4 years of age dropped by 20 per cent.2 In addition, the national surveillance data showed that the overall incidence reduced from 44/100 000 population in 1990 to 21/100 000 in 1997, during which about 54 per cent of all measles cases occurred in primary schoolchildren and 14 per cent in the intermediate and secondary schools.

Based on the above findings, the Ministry of Health of Saudi Arabia decided to implement the globally and regionally WHO recommended strategies to achieve measles and rubella elimination through implementing catch-up campaigns using MMR vaccine by targeting all schoolchildren. The first stage of the campaign was conducted in October 1998 targeting intermediate and secondary schoolchildren (13–18 years old), in which 1 629 565 students (96.4 per cent of the target students) were vaccinated. In January–February 2000, the second stage of the campaign was conducted by targeting all primary schoolchildren and first grade intermediate schoolchildren (6–13 years old), in which 2 412 078 students (96.6 per cent of the target students) were vaccinated.

Similar campaigns have been implemented in all Arabian Gulf countries: Oman and Kuwait in 1994, Bahrain in 1998–1999, United Arab Emirates in 1999, and Qatar in 2000.3 MMR vaccine has been shown to be associated with some adverse events that may follow some time after vaccination.4–10 Minor reactions that are occasionally seen following vaccination include fever, short-lasting respiratory symptoms, febrile convulsion, parotitis, and in rare cases other neurological complications. Aseptic meningitis, in some cases, occurs up to 42 days following the administration of the mumps vaccine, and in some cases the virus can be isolated in cell culture media inoculated with CSF and other clinical specimens.

In 1996 a large nationwide active surveillance in Japan found that the rates of virologically confirmed aseptic meningitis per 10 000 MMR doses were 16.6, 11.6, 3.2 and 0 for different Urabe strains.6 In the UK, Miller et al.7 stated that the true risk of post vaccination aseptic meningitis was substantially
higher (one in 11 000 doses) than suggested by paediatricians on a case-report basis. In France, the risk of aseptic meningitis assessed was around one case per 28 400 doses of the Urabe AM-9 mumps vaccine sold. In the city of Salvador in 1997, a mass immunization campaign with the Urabe containing measles–mumps–rubella vaccine, estimated a risk of the aseptic meningitis in vaccine recipients to be one in 14 000 doses. There is therefore a large discrepancy between the reported incidence following immunization with the Urabe-based mumps vaccine. This study has been designed to evaluate the adverse events that may be associated with the MMR vaccine containing the Urabe mumps strain in all primary schoolchildren that received the vaccine in the second phase of the catch-up campaign.

Materials and Methods

In the first stage of the sampling procedure eight cities were selected randomly: Mekkah and Medinah in the west, Buraïdah and Onaiza in the centre, Algatif and Al-Hofof in the east, and Khamis Mushait and Belغراراشي in the south.

In the second stage, all hospitals in the eight cities (19 hospitals) were included as a sampling frame for hospital-based surveillance and retrospective case-finding of post-MMR vaccination aseptic meningitis. In addition, 20 primary schools were selected from each city (10 male schools and 10 female schools) to conduct a school-based surveillance in order to review the absenteeism pattern.

The routine surveillance method for adverse events following immunization was supplemented by three additional surveillance methods.

Hospital-based surveillance

During a period of 10 weeks (starting from the 2nd day of the campaign) for any child in the age group 6–13 years diagnosed by a clinician as possible aseptic meningitis, three specimens (CSF, saliva and urine) were collected. These specimens were sent immediately from hospitals of the selected cities by courier to Riyadh and from there on the same day to the National Institute for Biological Standards and Control (NIBSC), UK, for virological and molecular characterization. Standard procedures drafted at NIBSC, of specimen collection, storage and transportation, were strictly applied during this study.

Retrospective case findings

As the national surveillance system records all cases other than bacterial meningitis as ‘other meningitis’, it was decided that these cases would not be included in the study. Instead, active case finding was conducted in all 19 hospitals to calculate the baseline data of aseptic meningitis cases. In each of the above selected hospitals, discharge reports of any child aged 6–13 years and with the final diagnosis of aseptic meningitis (specific or non-specific) on the paediatrics, medicine and neurology wards were reviewed. The review was conducted for the year preceding the campaign year.

School-based surveillance

In each of the 20 primary schools in the eight designated cities, absenteeism records of students were reviewed. All pupils that were recorded absent from school during the 2 weeks after vaccination were followed-up by primary healthcare physicians of the nearest health centre. Both school teachers and parents helped in determining the relation between absenteeism and MMR vaccination using a standard protocol prepared for this purpose.

Ethics

The study was evaluated and approved by the ethics committee of Ministry of Health, Saudi Arabia. The study was conducted in full compliance with the declaration of Helsinki III. All parents of participating children were given a full explanation of the study objective and design and gave consent voluntarily.

Results

Altogether six cases of aseptic meningitis were diagnosed clinically during the 10-week observation period following vaccination campaign. Four cases were recorded in two of the eight cities included in the study, and two cases were reported by a routine surveillance method from Riyadh, a city that was not part of the active surveillance programme. All, except one case, were Saudi children. Symptoms of aseptic meningitis were observed within 1–10 days of post-immunization in four cases, while in the other two cases symptoms were observed 20 and 61 days after vaccination, respectively.

Characterization of clinical specimens by mumps virus specific RT-PCR method, established previously at NIBSC by targeting the SH part of the genome, confirmed the presence of the mumps virus sequence in CSF of one patient. This was an 11-year-old Barmawi female who developed symptoms of aseptic meningitis 8 days after vaccination. Both saliva and urine samples of this patient were, however, negative by the RT-PCR detection method. A comparison of the nucleotide sequence of the SH gene generated from the CSF sample with the published sequence of the Urabe vaccine strain revealed that both sequences were almost identical to each other, with the exception of a single base change (data not shown). It has been shown previously that isolates derived from clinical specimens of Urabe vaccine recipients could accumulate one to two point mutations, in comparison to the progenitor vaccine virus, in the SH gene and other parts of the genome.
The length of stay in hospital for all cases ranged between 3 and 18 days with an average period of about 9 days. No complications were recorded in any of the cases during the 3-month follow-up period as all cases showed complete recovery (Table 1). Clinical manifestations recorded in all cases were fever and neck rigidity, vomiting and headache in five of the six cases observed. Other manifestations included muscle pain, fits and general weakness.

Active retrospective surveillance of the pre-MMR vaccination period of the eight cities identified 24 non-specific cases of aseptic meningitis. Of these 23 cases were not related to any vaccination regimes, as verified by examining the patients’ histories during a 6-week period prior to the symptoms onset. Only one case could be linked to DPT and OPV as the immunization with these vaccines was conducted 18 days before the onset of symptoms.

Absenteeism recorded during the 2 weeks post-MMR vaccination session in each school showed that altogether 1473 students were absent from schools, of whom 119 (8.4 per cent) students were absent (absenteeism rate = 26.5/10 000) due to adverse events following MMR immunization (AEFMI). These adverse events were mainly fever (20.3/10 000), parotitis (3.1/10 000), or both (2.7/10 000). The majority of adverse effects were recorded in female students (94.9 per cent), the reason for which is unknown. The incidence of fever was higher in the younger age group (6–9 years) while the incidence of parotitis was higher in the older age group (10–13 years) (Table 2 and 3).

### Table 1

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>PCR results</th>
<th>Hospital admission (days)</th>
<th>Complication</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAk1</td>
<td>Female</td>
<td>9</td>
<td>Negative</td>
<td>18</td>
<td>None</td>
<td>Dexamethazone, anti-convulsants</td>
</tr>
<tr>
<td>RYD2</td>
<td>Male</td>
<td>12</td>
<td>Negative</td>
<td>10</td>
<td>None</td>
<td>Antibiotics and analgesic</td>
</tr>
<tr>
<td>KHM1</td>
<td>Female</td>
<td>7</td>
<td>Negative</td>
<td>3</td>
<td>None</td>
<td>Antibiotics and analgesic</td>
</tr>
<tr>
<td>MAk2</td>
<td>Female</td>
<td>11</td>
<td>Positive</td>
<td>7</td>
<td>None</td>
<td>Ceftriaxone, paracetamol, and i.v. fluids</td>
</tr>
<tr>
<td>RYD1</td>
<td>Male</td>
<td>13</td>
<td>Negative</td>
<td>11</td>
<td>None</td>
<td>Antibiotics and analgesic</td>
</tr>
<tr>
<td>KHM2</td>
<td>Female</td>
<td>8</td>
<td>Negative</td>
<td>4</td>
<td>None</td>
<td>Antibiotics and analgesic</td>
</tr>
</tbody>
</table>

Discussion

This study is unique on the ground that MMR vaccine containing the Urabe mumps strain has never been evaluated for its safety aspects before, through an immunization campaign mainly conducted on previously vaccinated children. In this campaign about 92 per cent of children who received the vaccine had a primary dose of MMR vaccine at about 12 months of age. MMR vaccines of the Urabe and Jeryl Lynn mumps virus strains have been indiscriminately used for primary immunization in Saudi Arabia.

It is interesting to note that while the previous studies showed high incidences of aseptic meningitis following immunization with MMR containing Urabe strain of mumps virus, very few incidences were observed during this study. The estimated rate of vaccine-associated meningitis during the campaign was about one case per 295 000 doses. It is unlikely that this could be due to under reporting of cases as the active surveillance system adopted during the study was intensive and implemented vigorously. However, one of the possible explanations for the low reported post-vaccinal incidences is the presence of a very high proportion (92 per cent) of children in the study cohort that has documented records of primary immunization with MMR. If the existence of prior immunity to mumps has any effect(s) on the vaccine virus reactogenicity then it is possible to speculate that mumps vaccine of the Urabe strain is much less reactogenic when given as a booster dose rather than a primary dose. It is understandable that primed vaccine recipients may either contain sufficient levels of circulating anti-mumps antibodies, or immunological T-cell memory that would help the body to neutralize the virus before it could express its virulent effect(s). In another scenario it is also possible that vaccine-associated adverse events are probably more pronounced in toddlers (12-month-olds) than in the
older age group (6–13 years), where the immune system is more developed. Further investigations, however, are needed to support this assumption. It is documented that the mumps vaccine of the Urabe strain contains a sub-variant population of viruses that may have different reactogenic properties.\(^{15–17}\) If during the vaccine development stage different preparations of seed virus were produced and they differed from each in terms of residual variant virus composition, then it is conceivable that vaccine produced from one seed stock may differ from another seed stock in terms of reactogenicity and immunogenicity. However, in collaboration with the Urabe vaccine producers this needs to be demonstrated experimentally.

A short length of stay in hospitals (average 9 days), a lack of complications during the 3-month follow-up period, and a complete recovery of all cases proved that clinical manifestation of aseptic meningitis following MMR vaccination was mild in clinical terms.

With regard to the retrospective case findings phase of the study it shows that although 24 non-specific aseptic meningitis cases were identified, none of them bears any causal association with MMR vaccine. What caused the disease in these children remains to be investigated through laboratory test and other clinical procedures. In the absence of such data the negative results should be read cautiously.

The surveillance system applied at primary school levels in all study areas revealed that only 119 MMR vaccinated students (26.5/10 000) developed symptoms related to MMR vaccination. There were no long-term sequelae and thus the reported adverse events could easily be classified as ‘mild events’, which will probably be seen following any immunization campaign of this scale. However, the benefits of the immunization campaign significantly outweigh the risks seen in a handful of children during the campaign in terms of protecting over two million children against three serious childhood infectious diseases, namely measles, mumps and rubella. This observation will also enhance the feasibility of implementing a measles and rubella control/elimination programme in Saudi Arabia. The study also demonstrates the importance of using different surveillance methods and concludes that routine EPI surveillance to monitor adverse events following immunization should be supplemented by an active surveillance method to ascertain the vaccine’s safety and efficacy.

It is also clear from this study that an active surveillance system to monitor cases of aseptic meningitis should be established and implemented vigorously in Saudi Arabia.

### References


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### Table 2

| Characters of absenteeism during MMR vaccination campaigns for primary schoolchildren, January–February 2000, Kingdom of Saudi Arabia |
|---|---|---|---|---|---|
| Absenteeism due to AEFI | Male | | | Female | |
| Sex | Age group | No. | Incidence rate | No. | Incidence rate | No. | Incidence rate | No. | Incidence rate |
| | 6–9 years | 10–13 years | | | | | | | |
| Male | 91 | 20.3 | | 14 | 3.1 | | 12 | 2.7 | | 2 | 0.4 | | 119 | 26.5 | |
| Female | 2 | 0.9 | | 2 | 0.9 | | 2 | 0.9 | | 0 | 2.7 | | 6 | 2.7 | |
| No. Incidence rate | | | | | | | | | |

Incidence rate/10 000 students.

### Table 3

| Adverse events following MMR immunization recorded in primary schoolchildren, January–February 2000, Kingdom of Saudi Arabia |
|---|---|---|
| Reason for absenteeism | Number of students | Absenteeism rate/10 000 students |
| | | |
| Due to adverse events following MMR immunization | 119 | 26.5 |
| Due to other medical causes | 942 | 210.1 |
| Due to non-medical causes | 412 | 91.9 |
| Total absenteeism | 1473 | 328.6 |

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Journal of Tropical Pediatrics Vol. 48 December 2002