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Effect of age on the incidence of aseptic meningitis following immunization with monovalent mumps vaccine

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ABSTRACT

Objective: The purpose of this study was to determine the risk of aseptic meningitis after mumps vaccination in younger children compared with older children.
Methods: This prospective cohort study included a total of 21,465 children under 18 years of age who had received the first dose of three of the Japanese mumps monovalent vaccine. We compared the cumulative incidence of aseptic meningitis for 30 days after vaccination among the following age groups: ≤1, 2, 3–4, and ≥5 years old. We also investigated the cumulative incidence of salivary gland swelling, a fever (≥38 °C) lasting at least 3 days during the 10 to 25 days following immunization, vomiting of 3 times or more, headache, and seizure.
Results: A total of 10 aseptic meningitis, 551 salivary gland swelling, 844 fevers, 669 vomiting, 757 headaches, and 29 seizure cases were identified. The cumulative incidence of aseptic meningitis increased with age (0.016%, 0.021%, 0.066%, and 0.096%, respectively). Statistical significance was observed between children ≥3 years old and those <3 years of age [0.078% vs. 0.018%, RR 4.35 (95% CI 1.05–18.2), $p = 0.04$]. The cumulative incidence of salivary gland swelling also increased with age (1.8%, 3.0%, 3.5%, and 4.5%, respectively). For non-specific adverse events, the cumulative incidence of fever or seizure decreased with age. In contrast, the cumulative incidence of headache increased with age. The cumulative incidence of vomiting was similar among children ≤4 years of age; however, that in those children ≥5 years old was significantly lower.
Conclusions: The first dose of mumps vaccine that is currently available for use in Japan may be administered in children less than 3 years of age in order to complicate a less aseptic meningitis after immunization.

In Japan, a standard measles–mumps–rubella (MMR) vaccine that used AIK-C measles strain, Urabe Am9 mumps strain, and the To336 rubella strain was added to the routine immunization program in April 1989 [1]. Shortly thereafter, a number of cases of postvaccine aseptic meningitis were reported. In October 1989, the Ministry of Health and Welfare conducted nationwide monitoring for postvaccine aseptic meningitis, and reported that the rate was 0.16%. In October 1991, in addition to the standard vaccine, three other MMR vaccine [Takeda MMR vaccine (measles-Schwarz FF8, mumps-Torii, rubella-To336), Kitasato MMR vaccine (measles-AIK-C, mumps-Hoshino, rubella-Takahashi), and the Research Foundation for Microbial Diseases of Osaka University (Biken) MMR vaccine (measles-Tanabe, mumps-Urabe Am9, rubella-Matsuura)] became available for the routine immunization program. However, a large number of postvaccine aseptic meningitis cases continued to be reported. Finally, the Ministry of Health, Labor and Welfare recommended the suspension of all MMR vaccinations and the mumps vaccine was excluded from the routine immunization program in April 1993. As a result, the estimated vaccination rate has remained low (about 30%) [2], and mumps is consequently still endemic in Japan [3].

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Table 1
Characteristics of the vaccine recipients stratified by age.

Characteristics	≤1 y (*n* = 6443)	2 y (*n* = 4777)	3–4 y (*n* = 6064)	≥5 y (*n* = 4181)	*p*
Boy, *n* (%)	3427 (53%)	2572 (54%)	3242 (53%)	2478 (59%)	<0.001
Strain, *n* (%)					
Torii	2512 (39%)	1620 (34%)	2216 (37%)	1502 (36%)	<0.001
Miyahara	2201 (34%)	1542 (32%)	1769 (29%)	1246 (30%)	
Hoshino	1727 (27%)	1613 (34%)	2076 (34%)	1431 (34%)	
Unknown	3 (0.05%)	2 (0.04%)	3 (0.05%)	2 (0.05%)	
Complete response of daily diary, *n* (%)	5452 (85%)	3939 (82%)	5052 (83%)	3399 (81%)	<0.001

It has also been reported that the risk of aseptic meningitis after vaccination with the currently available mumps monovalent vaccines in Japan is less frequent than that of wild mumps virus infection [4]. In order to determine the safety of all available mumps monovalent vaccines in Japan, we hypothesized that the risk of adverse events, such as aseptic meningitis, is lower in younger children than in older children. This is because subclinical infections are more common and complications are less frequent in younger children during mumps virus infection [5,6]. In this study, we compared the cumulative incidence of adverse events, in particular aseptic meningitis, using our previous reported data.

1. Methods

1.1. Study design and participant population

This was a prospective cohort study. The subjects and methods of the cohort follow-up have been described previously [4]. In brief, all children under 18 years of age were eligible to be enrolled by the 143 pediatric practitioners if they had received the mumps vaccine during the study period, from January 1, 2000 to January 1, 2003. Three Japanese licensed mumps vaccine strains were used: Torii (Takeda Pharmaceutical Company Limited), Miyahara (Kaketsuken, the Chemo- Sero-Therapeutic Research Institute), and Hoshino (Kitasato Institute, Research Center for Biologicals). Parents or guardians were asked to monitor the signs and symptoms of adverse events, including body temperature, vomiting, headache, seizure, and salivary gland swelling, and complete a standardized daily diary for a 30-day period after immunization. Parents or guardians were asked to take the children's body temperature before going to bed. Fever in this study was defined as a body temperature ≥38 °C lasting at least three days during the 10 to 25 days following immunization. Vomiting was defined as three times or more during the course of illness [1,7].

1.2. Diagnosis of postvaccine aseptic meningitis

A lumbar puncture to obtain cerebrospinal fluid was performed in the patients whose symptoms were suggestive of aseptic meningitis and were judged to be severe enough to warrant hospitalization by their physicians. Aseptic meningitis was defined as cerebrospinal fluid pleocytosis of greater than 15 white blood cells observed. After diagnosing aseptic meningitis, the cerebrospinal fluid was frozen and transferred to the clinical laboratory at the Kitasato Institutes on dry ice within 48 h after sampling. Mumps virus infection was confirmed by positive virus isolation in Vero cells and/or by the detection of the mumps virus genome through nested real time-PCR [8,9]. Nested PCR was performed targeting the part of genome regions of the phosphoprotein and/or hemagglutinin–neuraminidase gene [10–14]. Genomic differentiation of the vaccine strain from wild strains was performed by a sequence analysis of the phosphoprotein and hemagglutinin–neuraminidase genes in all hospitalized meningitis cases [9–11,15,16]. We purified the PCR products and analyzed the DNA sequences bidirectionally with a Dye Terminator Sequencing Kit (Applied Biosystems Japan Inc., Tokyo, Japan) using an automated nucleotide analyzer (377A DNA Sequencer, Applied Biosystems, Foster City, CA, USA).

1.3. Statistical analysis

The vaccine recipients were categorized into the following age groups: ≤1, 2, 3–4, and ≥5 years old. The rationale for using these 4 age groups was to divide the studied numbers of patients equally. To examine the effect of age at vaccination on the risk of adverse events, we compared the cumulative incidence of adverse events among the age groups. We also calculated relative risk (RR), and 95% confidence interval (CI). Due to the limitation of our sample size, in particular for aseptic meningitis cases, we also compared the cumulative incidence between the groups of children <3 years and ≥3 years of age. For specific adverse events of the mumps vaccine, we compared those of aseptic meningitis and salivary gland swelling cases. For non-specific adverse events, we compared those of a fever, vomiting, headache, and seizure. We also compared the cumulative incidence of cases of a prolonged fever with vomiting and/or headache, which may sometimes be a milder form of aseptic meningitis [1,7].

The differences in the cumulative incidence of adverse events were compared with Fisher's exact test. We also performed stratified comparisons using Mantel–Haenszel statistics to adjust for sex because male sex has been shown to be a risk for neurological manifestations following mumps virus infection [6,17]. Analyses were conducted using the SPSS software package, version 17.0 (SPSS Inc., Chicago, IL, USA).

2. Results

2.1. Characteristics of the vaccine recipients stratified by age

A total of 21,465 children under 18 years of age who had received the first dose of a mumps monovalent vaccine were studied; 7850 children were immunized with the Torii strain, 6758 with the Miyahara strain, and 6847 with the Hoshino strain. The particular strain used to immunize the remaining 10 children was unknown. The median age at vaccination was 2 years old. Table 1 shows the characteristics of vaccine recipients stratified by age. The proportion of boys in the ≥5 years old group [59% (2478/4181)] was slightly higher than that in the other age groups. The proportion of recipients vaccinated with the Hoshino strain in the ≤1 year group [27% (1727/6443)] was slightly lower than that in the other age groups. The proportion of responders of the daily diary completely in the ≤1 year group [85% (5452/6443)] was slightly higher than that in the other age groups.

2.2. Aseptic meningitis and salivary gland swelling stratified by age

A total of 10 aseptic meningitis cases were reported. The mumps virus genome was detected by nested real time-PCR, and the genome of the vaccine strain was identified in eight patients. No etiological agent was identified in the other two

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