Mumps vaccine virus strains and aseptic meningitis

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Abstract

Mumps immunization can easily be included in national schedules, particularly if combined with measles or measles and rubella vaccines, but debate continues concerning the relative safety of various licensed mumps vaccine strains. The opportunities for control of mumps are also being affected by differences in the cost of the vaccines prepared with different strains of mumps virus. The present report evaluates available data on the association of the Urabe and other strains of mumps vaccine with the occurrence of aseptic meningitis. We also review the comparative immunogenicity and efficacies of the most widely used mumps vaccines in controlled clinical trials and field evaluations, and briefly examine relative cost as it relates to the implementation of national immunization programs. We conclude that extensive experience with the most widely used mumps vaccine strains in many countries has shown that the risk–benefit ratio of live mumps vaccines is highly favourable for vaccination, despite the occasional occurrence of aseptic meningitis.

Keywords: Mumps vaccines; Aseptic meningitis; Urabe

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Keywords: Mumps vaccines; Aseptic meningitis; Urabe

References

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1. Introduction

Few public health interventions have averted more deaths and illness than vaccines used in systematically designed immunization programs. Mumps immunization can easily be included in national schedules, particularly if combined with measles or measles and rubella vaccines. To date over 500 million doses of mumps vaccines have been administered, mainly in industrialized countries. Approximately 120 countries currently use mumps vaccines in their national immunization services [1]. However, debate continues concerning the safety profiles of the various licensed mumps vaccine strains. The opportunities for control of mumps are also being affected by differences in the cost of the vaccines prepared with the different strains of mumps virus [2]. The present report evaluates available data on the association of the Urabe and other strains of mumps vaccine with the occurrence of aseptic meningitis. We also review the comparative immunogenicity, efficacy, and persistence rates of various mumps strains in controlled clinical trials, and briefly examine relative cost as it relates to the implementation of national immunization programs.

2. Methods

We searched the Medline database for primary publications evaluating the association of aseptic meningitis with mumps vaccination. We included both prospective and retrospective evaluations, controlled trials and observational studies of measles–mumps–rubella (MMR) combination vaccines in populations sufficiently large to allow an estimate of incidence. Studies evaluating Urabe, Leningrad-Zagreb, Jeryl Lynn and Jeryl Lynn-derived vaccines were included, since these are the ones most widely used. We also searched the references of the retrieved papers for additional studies that met the above criteria.

3. Mumps: the disease

Mumps is an acute viral infection primarily affecting the salivary glands. Although mumps is considered a mild, self-limiting, childhood disease, infection also occurs in adolescents and adults, usually with more severe complications than in infants and children. One of the most frequent complications of natural mumps infection is aseptic meningitis, which occurs in up to 10% of individuals not only in children, but also in adults [3]. Aseptic meningitis is a self-limiting disease characterized by the sudden onset of fever with signs and symptoms of meningeal involvement as evidenced by changes in cerebrospinal fluid, including pleocytosis, and an absence of bacteria. Treatment is symptomatic and the majority of patients recover within 1 week [4]. Other complications of mumps infection include orchitis, oophoritis, pancreatitis, mastitis, nephritis, hearing impairment, and encephalitis. Arthropathy and myocarditis associated with mumps infection have been observed infrequently [1,3].

The worldwide annual incidence of mumps ranges from 100 to 1000 per 100,000 of the general population, with epidemic peaks every 2–5 years. The peak incidence is found among children 5–9 years of age. Natural infection with mumps virus is thought to confer lifelong protection [1]. Before mumps vaccine became available, nearly every child became infected with the mumps virus. Although the number of cases is currently much lower than during the prevaccination era, children who are not immunized are still likely to become infected with the disease. Recent outbreaks of mumps in the United Kingdom and the United States underline the need for vaccination.

4. Mumps vaccines

All commercially available mumps vaccines contain live attenuated virus, and may be monovalent, but are usually given in combination with measles and rubella vaccines (MMR), according to recommendations from the World Health Organization (WHO) [5]. An estimated 500 million doses of mumps vaccine have been administered, mainly in industrialized. Where sustained vaccination has been accomplished, the incidence of mumps has been significantly reduced. In general, adverse reactions to mumps vaccines are rare and mild [1,5].

More than 10 mumps vaccine strains have been used in various countries throughout the world (Table 1) [6]. The Biken Institute in Japan developed the Urabe Am9 strain from mumps virus isolated from the saliva of a patient. The Urabe virus strain of live mumps vaccine was first licensed in Japan and thereafter in Belgium, France, and Italy, and many other countries worldwide. It is produced either in the amniotic fluid of embryonated hens’ eggs or in chick embryo cell cultures and has been used successfully, along with vaccines containing Jeryl Lynn, Jeryl Lynn derived, and Leningrad-Zagreb mumps virus strains. Other licensed mumps strains have more limited distribution.

The Jeryl Lynn strain is named for the patient from whom it was originally isolated. It also was the first vaccine strain to be developed by successive passage in embryonated hens’ eggs and chick embryo cell cultures. At the initial level of attenuation, the Jeryl Lynn strain caused parotid swelling in some vaccine recipients, indicating that the vaccine strain was not sufficiently attenuated. Additional passages eliminated the parotid swelling, and since 1967, a live attenuated Jeryl Lynn vaccine has been used in many countries. The RIT 4385 strain was developed from a Jeryl Lynn clone (JL-1) by passage through chick embryo fibroblast cultures [3].

The Leningrad-3 strain was developed in the USSR in the 1950s in guinea pig kidney cell culture, with further passages in Japanese quail embryo cultures. Vaccines based on this strain have been used in the former Soviet Union and other countries. The Leningrad-3 mumps virus was further
Table 1
Mumps vaccine strains currently in use

<table>
<thead>
<tr>
<th>Strain</th>
<th>Manufacturer</th>
<th>Cell substrate</th>
<th>Main area of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeryl Lynn</td>
<td>Merck</td>
<td>CEF</td>
<td>Worldwide</td>
</tr>
<tr>
<td>RIT 4385a</td>
<td>GlaxoSmithKline</td>
<td>CEF</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Urabe</td>
<td>Sanofi Pasteur</td>
<td>CEF</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Hoshino</td>
<td>Biken</td>
<td>CEF</td>
<td>Japan</td>
</tr>
<tr>
<td>Rubini</td>
<td>Swiss Serum Institute</td>
<td>CEF</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Leningrad-3</td>
<td>Bacterial Medicine Institute, Moscow</td>
<td>HDCS</td>
<td>Russia</td>
</tr>
<tr>
<td>Leningrad-Zagreb</td>
<td>Institute of Immunology of Zagreb</td>
<td>CEF</td>
<td>Yugoslavia</td>
</tr>
<tr>
<td>Miyahara</td>
<td>Chem-Sero Therapeutic Research Institute</td>
<td>CEF</td>
<td>Japan</td>
</tr>
<tr>
<td>Torii</td>
<td>Takeda Chemicals</td>
<td>CEF</td>
<td>Japan</td>
</tr>
<tr>
<td>NK M-46</td>
<td>Chiba</td>
<td>CEF</td>
<td>Japan</td>
</tr>
<tr>
<td>S-12</td>
<td>Razi State Serum and Vaccine Institute</td>
<td>HDCS</td>
<td>Iran</td>
</tr>
</tbody>
</table>

CEF: chick embryo fibroblast; HDCS: human diploid cell strain.

a Derived from Jeryl Lynn strain.

attenuated in Croatia by adaptation and passages on chick embryo fibroblast cell cultures. The new mumps strain, designated L-Zagreb, is used in Croatia and India [3]. Although the attenuated virus strains used in the available vaccines result in substantially fewer neutralizing mumps antibodies compared to natural infection vaccination is very effective [7].

5. Postvaccine aseptic meningitis

Meningitis is one of the most frequent complications of natural mumps infection [8,9]. Attenuated mumps virus strains used in vaccines have lost most of their potential for meningitis as a complication of viremia, but this potential has not been lost entirely. The reported rate of aseptic meningitis that occurs after vaccination ranges widely, from approximately 1 in 1.8 million doses for the Jeryl Lynn strain [10] to as high as 1 in 1000 for the Leningrad-3 strain [11]. Postvaccinal aseptic meningitis, if it occurs, usually does so between 2 and 3 weeks after vaccine administration. There is not yet a clear consensus on the definition of this condition. The American Centers for Disease Control and Prevention defines postvaccine aseptic meningitis as a syndrome characterized by the acute onset of meningeal symptoms, fever, and cerebrospinal fluid pleocytosis, with bacteriologically sterile cultures [12]. The Brighton collaboration is attempting to develop a consensus case definition of aseptic meningitis that will be widely accepted. This would make comparison of clinical study data from different clinical trials easier and increase the diagnostic certainty of reported adverse events following immunization [13]. Confirmation of the causative role of vaccine virus requires definitive identification of the mumps virus isolate as the vaccine strain. However, because viruses similar or identical in sequence to the vaccine virus previously administered have been isolated from people with postvaccination meningitis, there is no doubt that some vaccine strains can cause meningitis [14].

As is the case for aseptic meningitis from wild mumps virus infection, postvaccine aseptic meningitis is observed more frequently in males than in females. In contrast to natural mumps disease with a known risk of encephalitis, leading in some cases to permanent disability or death, complications of postvaccine aseptic meningitis are generally of mild to moderate intensity and resolve spontaneously within 1 week with no reported sequelae [15]. More recently, the WHO Global Advisory Committee on Vaccine Safety stated in June 2003 that “all reported cases of vaccine-derived mumps meningitis have recovered” and that “there is no known case with long-term sequelae” [16].

6. Evaluations of vaccination-associated aseptic meningitis

6.1. Urabe mumps virus strains

Prior to 1989, worldwide passive postmarketing surveillance data indicated that vaccination-related mumps meningitis occurred after fewer than 1 in 100,000 vaccine doses [17]. Active surveillance data disclosed an incidence of Urabe strain vaccine-related meningitis of approximately 1 in 233,000 doses [17]. The Urabe AM9 strain consists of a mixture of mumps viruses that differ at a single codon of the hemagglutinin-neuraminidase gene. Genetic studies indicate that all Urabe AM9 vaccines strains may not be the same, thus, leading to vaccines with different reactogenicity profiles [18,19].

The first reports suggesting a relationship between Urabe-containing mumps vaccines and the occurrence of aseptic meningitis appeared in 1989, with eight cases of virally confirmed postvaccine aseptic meningitis in Canada, with an estimated incidence of 1/62,000 doses administered [20,21]. Following the North American reports, active surveillance in the United Kingdom revealed a cluster of cases in the Nottingham area. An investigation that linked virology
laboratory and hospital discharge records with vaccination histories found one case of postvaccination meningitis per 3800 doses of MMR administered in the Nottingham health district [22]. During this period, 80% of the MMR used in the district contained the Urabe strain, and all cases of meningitis identified followed inoculation with vaccines that contained the Urabe strain [22]. Subsequent Public Health Laboratory Service surveillance data for 13 additional United Kingdom health districts, suggested a rate of one case of aseptic meningitis per 11,000 doses among children 12–24 months of age who received Urabe-containing vaccine [23]. The active surveillance conducted by Miller and colleagues identified 13 cases of aseptic meningitis, and while virus was identified in only five of these patients, the investigators concluded that high leukocyte counts in the CSF plus the temporal association with vaccination indicated a causative association. In addition, the occurrence of aseptic meningitis at four independent sites supported the view that the cases diagnosed earlier in the series in Nottingham were not a chance cluster [23]. Although it may be argued that the study design and methods reduced the precision of the estimated incidence of postvaccinal aseptic meningitis in the UK series, the results do show the incidence to be higher than previously thought [17,23,24]. Following these findings, vaccines containing the Urabe strain were withdrawn from use in the UK, Canada, and several other countries. In light of the results reported in the UK and Canadian studies, a number of other evaluations were performed to assess the risk of postvaccine aseptic meningitis following vaccination with MMR vaccines containing different mumps virus strains. It is clear from the available data that rates of postvaccine aseptic meningitis vary according to the vaccine strain, the manufacturer, the index of clinical suspicion, and the intensity of surveillance.

As seen in Table 2, the rates of postvaccine aseptic meningitis vary among the Urabe strains. For the Urabe Am9 vaccine produced by Sanofi Pasteur, a cross-comparison of data from a national network and hospital virology laboratories (EPIVIR) using the capture–recapture method assessed this risk to be 1 case per 28,400 doses (95% CI: 18,000: 67,200) [25]. In a retrospective survey requested by the French Ministry of Health, the global incidence of vaccine-associated aseptic meningitis was 0.82 per 100,000 doses [26]. During the year 2000, 2.4 million children 6–13 years of age were immunized during a vaccination campaign

### Table 2

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Country</th>
<th>Rate (N)</th>
<th>Type of study and surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al. [23]</td>
<td>UK</td>
<td>1/11,000 (78,300)</td>
<td>Retrospective: cerebrospinal fluid evaluation in children discharged with diagnosis of aseptic or viral meningitis within 15–35 days after MMR vaccination; 4 of 13 cases virus positive</td>
</tr>
<tr>
<td>Farrington et al. [24]</td>
<td>UK</td>
<td>1/15,000 (77,200)</td>
<td>Retrospective: linkage of vaccination records and hospital discharge for aseptic or viral meningitis</td>
</tr>
<tr>
<td>Jonville-Bera et al. [26]</td>
<td>France</td>
<td>1/121,951</td>
<td>Retrospective: passive surveillance: 4 of 54 cases with laboratory confirmation of mumps virus in cerebrospinal fluid</td>
</tr>
<tr>
<td>AI-Mazrou et al. [27]</td>
<td>Saudi Arabia</td>
<td>1/295,000 (est. 2,000,000)</td>
<td>Prospective: active surveillance following booster vaccination in a “catch-up” campaign; six cases confirmed</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furesz and Contreras [21]</td>
<td>Canada</td>
<td>1/62,000</td>
<td>Retrospective: passive surveillance eight cases with virologic confirmation</td>
</tr>
<tr>
<td>Dourado et al. [33]</td>
<td>Brazil</td>
<td>1/14,000 (est. 450,000)</td>
<td>Prospective: passive surveillance of hospital admissions for AM. 32 cases/452,344 doses</td>
</tr>
<tr>
<td>Other manufacturers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujinaga et al. [29]</td>
<td>Japan</td>
<td>1/336 (11,750), 1/904 Lab confirm</td>
<td>Retrospective: passive surveillance</td>
</tr>
<tr>
<td>Sugiura and Yamada [30]</td>
<td>Japan</td>
<td>1/6564 (630,157)</td>
<td>Retrospective: surveillance by physicians; 96 cases with viral confirmation</td>
</tr>
<tr>
<td>Kimura et al. [31]</td>
<td>Japan</td>
<td>(38,203)</td>
<td>Prospective: active surveillance by parents. Virologically confirmed cases/vaccinees:</td>
</tr>
<tr>
<td>Vaccine:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takeda</td>
<td></td>
<td>1/860</td>
<td>10/8600</td>
</tr>
<tr>
<td>Kita</td>
<td>1/3120</td>
<td>0</td>
<td>7/21,717</td>
</tr>
<tr>
<td>Kitasato, Biken</td>
<td></td>
<td>1/604</td>
<td>0/3054</td>
</tr>
<tr>
<td>Ki et al. [32]</td>
<td>Korea</td>
<td>1/10,500 (324,000)</td>
<td>Retrospective, case-crossover study; 34 cases after 324,000 vaccine doses.</td>
</tr>
</tbody>
</table>

* At the time of the study, Urabe vaccines manufactured by both Sanofi Pasteur (then Aventis Pasteur) and GlaxoSmithKline were licensed, and it is not possible to relate occurrence of postvaccine aseptic meningitis to a specific vaccine.

* The rate of 1/28,400 is based on an estimate of 116 cases of postvaccine aseptic meningitis by the capture–recapture method. The actual number of observed cases was 46, and no virus isolation was carried out. The rate calculation using the number of observed cases is 1/65,750.

* Patients were given either Urabe (various manufacturers not specified, but included Urabe strain from Sanofi Pasteur) or Hoshino strain vaccine.
in Saudi Arabia using the Sanofi Pasteur vaccine [27]. Hospital-based surveillance data showed that the incidence of postvaccine aseptic meningitis was 1 per 295,000 doses. The authors suggested that this exceptionally low rate of postvaccine aseptic meningitis might have occurred because nearly all of these children had already received primary immunization against MMR at 12 months of age and, therefore, were not immunologically naïve.

Occurrence of aseptic meningitis was prospectively evaluated in a randomized, double-blind study in over 10,000 Brazilian students between 6 and 12 years of age. Subjects received MMR combinations containing Urabe AM9 (Sanofi Pasteur), Leningrad-Zagreb (Serum Institute of India), or Jeryl Lynn (Merck) mumps vaccine. Three cases of aseptic meningitis occurred during the 30-day follow-up period, only one of which was related vaccination, and it occurred in the Leningrad-Zagreb group, corresponding to one case per 2226 doses. Because of the small sample size, the rate of occurrence could not be used to calculate a reliable estimate of incidence [28].

In Japan, rates of aseptic meningitis after vaccination with the Urabe strain have been reported to be as high as 1 in 2000 doses, and the rate of meningitis with Urabe strain isolated from cerebrospinal fluid as 1 in 9000 doses [29]. In one prefecture, the rate of proven Urabe-related aseptic meningitis was 1 in 900 [30]. A subsequent prospective study of meningitis after vaccination with Urabe-containing MMR vaccines produced by four different Japanese manufacturers yielded results that were different for each vaccine. Urabe vaccine manufactured by Biken gave an incidence of 25 per 10,000 doses administered in one formulation but no cases were reported per 10,000 doses in another formulation. The rates for Urabe vaccines made by Takeda and Kitasato were 14 and 7.4 per 10,000 doses administered, respectively [31].

A retrospective case-crossover study conducted in Korea, estimated a rate of aseptic meningitis following vaccination administration of 1 in 10,500 doses, but could not differentiate between the effects of the Urabe and Hoshino strains as both had been given [32]. Finally, a case–control analysis in Salvador, Brazil showed an attributable risk of meningitis of 1 in 14,000 doses following a mass vaccination campaign with MMR vaccine containing Urabe virus [33].

6.2. Jeryl Lynn and Jeryl Lynn-derived mumps virus strains

The Jeryl Lynn strain is associated with the lowest incidence of postvaccine aseptic meningitis (Table 3). In the United States, Black et al. attempted to assess the level of increased risk of hospitalizations for aseptic meningitis after administration of MMR vaccine containing the Jeryl Lynn mumps strain in the Vaccine Safety Datalink (VSD) population [34]. The VSD project linked outcome and vaccine exposure information for 500,000 children younger than 7 years of age in Northern California. This retrospective case–control study analyzed the first 2 years of available data in ascertaining the possible risk of postvaccine aseptic meningitis. Of the 59 cases of aseptic meningitis that were identified, only 2 had an apparent onset within 30 days of receiving the Jeryl Lynn mumps vaccine. In other retrospective studies in the US and Finland, no cases of postvaccine aseptic meningitis were identified [35–37]. An analysis of spontaneously reported side effects after 14 years of use in Germany reported 0.1 case per 100,000 doses administered [38].

There are few data from studies of Jeryl Lynn-derived mumps strains. In the study by Schlipkoter et al., the risk of aseptic meningitis after Jeryl Lynn-derived mumps vaccination was estimated to be <1/525,312 [39]. A meta-analysis compiled data from eight prospective, randomized, single-blind studies in six countries enrolling a total of 4702 children, aged 9–24 months, who received either Jeryl Lynn or Jeryl Lynn-derived vaccine. Suspected meningitis/febrile convulsions were reported in 4 children within 42 days following vaccination. A lumbar puncture was performed in 1 subject and the cerebrospinal fluid was normal. Although in the absence of a lumbar puncture, aseptic meningitis cannot be excluded, the available data in the remaining three cases were consistent with a diagnosis of convulsions secondary to fever [40].

6.3. Leningrad-Zagreb mumps virus strain

In 1997, the Bahamas conducted a mass MMR vaccination campaign, immunizing over 100,000 people between the ages of 4 and 40 years. All but 5000 doses included a vaccine containing a Leningrad-Zagreb strain mumps vaccine. Active surveillance reported one case of vaccine-related aseptic meningitis, giving an incidence of 0.96 per 100,000 vaccinees [41]. In other studies, conducted in Brazil, incidences of aseptic meningitis were higher. One study, in which over 840,000 doses of vaccine were given to children in two provinces estimated that the vaccine elicited 1 case for each 6000 to 19,000 doses given [42]. Another study estimated an incidence of 1 case of aseptic meningitis per 3390 doses of L-Zagreb mumps vaccine [43]. Finally, in a large vaccine campaign, 590,609 people, aged from 1 to 39 years, were vaccinated with L-Zagreb mumps vaccine. After vaccination, 87 cases of aseptic meningitis were reported, giving an incidence of 1.7 cases per 10,000 doses [44]. The differences in incidence of aseptic meningitis observed in these studies have recently been reviewed. The influence of case definition, quality of surveillance, and study design on the estimated incidence rates of aseptic meningitis in the Brazilian trials, and the importance of distinguishing cases caused by wild versus vaccine viruses, are discussed [45].

7. Immunogenicity, efficacy

Whereas it is accepted that the Urabe strain-containing MMR vaccines are associated with a higher incidence of postvaccine aseptic meningitis compared with Jeryl Lynn or
Jeryl Lynn-derived strains, it is important to note that there are differences in the immunogenicity and efficacy of the different mumps strains. As seen in a number of studies performed in various countries, the Urabe-containing mumps vaccine generally had the highest effectiveness of the available mumps vaccine strains. In contrast, the Rubini strain, developed by passage in a human diploid cell line, serial passaging in embryonated hen’s eggs, and then adapted to the MRC-5 human diploid cell line, has lower efficacy than vaccines containing Urabe or Jeryl Lynn strains [1]. A 3-year comparative study in Switzerland demonstrated that the Rubini strain conferred only 6.3% protection, whereas the Urabe- and Jeryl Lynn-containing vaccines achieved 73.1% and 61.6% efficacy rates, respectively [1]. A case–cohort study during a mumps outbreak in Switzerland in 1999 and 2000 reported that the Rubini vaccine resulted in a vaccine efficacy rate of 29% compared with 71% for the Jeryl Lynn vaccine [46]. The authors concluded that the Rubini vaccine is inappropriate for the control and elimination of mumps and its use should be discontinued.

The results of several comparative studies of the immunogenicity and the efficacy or effectiveness of Jeryl Lynn and Urabe strain vaccines are summarized in Tables 4 and 5. Serologic studies show high response rates to Jeryl Lynn-containing vaccines from the age of 12 months. For the Urabe strain, high titres are achieved from the age of 9 months [1]. Overall seroconversion rates with the Urabe strain were consistently higher than with the Jeryl Lynn strain (84–97% versus 63–96%, respectively) [46–50]. Likewise, overall efficacy rates were consistently higher with the Urabe strain than with the Jeryl Lynn strain (73.1–97.9% versus 61.6–93.8%, respectively) [46,51–54].

Several noncomparative studies evaluating the immunogenicity of the Urabe vaccine in developing countries have been discussed in a review publication [55]. Among seronegative children who received the Urabe vaccine at 9 months of age, seroconversion rates of 99% in Brazil, 98% in South Africa, and 75% in India have been observed. Among seronegative children vaccinated at 12 months of age, seroconversion rates of 100%, 98%, and 92% have been reported in studies conducted in Brazil, Taiwan, and India, respectively. In a South African study the response rate at 15 months of age was 100%, and in a study from Taiwan, the response rate was 98% at 14–18 months of age. Few studies of the Jeryl Lynn vaccine have been conducted in developing countries. However, a study in the Dominican Republic reported a 94% seroconversion rate among 72 seronegative children aged 1–6 years.

Long-term follow-up studies suggest that decline of antibody concentration after mumps vaccination occurs more quickly with the Jeryl Lynn strain than with the Urabe strain. In the United Kingdom, Miller et al. showed that 4 years after MMR vaccination in children 12–18 months of age, the seronegativity rates were 19% in Jeryl Lynn recipients versus 15% in Urabe recipients, a statistically significant difference [56]. Similarly data were reported by a study conducted in

### Table 3
Reported incidence of postvaccine aseptic meningitis following vaccination with MMR vaccines containing Jeryl Lynn-derived mumps virus

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Rate (N)</th>
<th>Type of study and surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fescharek et al. [38]</td>
<td>Germany</td>
<td>1/1,000,000</td>
<td>Retrospective case series (1/5 cases in 15–35-day interval)</td>
</tr>
<tr>
<td>Schlipkoter et al. [39]</td>
<td>&lt;1/525,312 Jeryl Lynn-derived</td>
<td>Retrospective: active surveillance 8 cases in 15–35-day interval (5/1,907,875 Jeryl Lynn doses; 3/1,575,936 Jeryl Lynn-derived doses)</td>
<td></td>
</tr>
<tr>
<td>Black et al. [34]</td>
<td>USA</td>
<td>1/150,000</td>
<td>Retrospective: passive surveillance</td>
</tr>
<tr>
<td>Davis et al. [35]</td>
<td>USA</td>
<td>0/18,036 (4–5 years of age)</td>
<td>Retrospective: passive surveillance</td>
</tr>
<tr>
<td>Patja et al. [36]</td>
<td>USA</td>
<td>0/1,800,000</td>
<td>Retrospective: passive surveillance</td>
</tr>
<tr>
<td>Makela et al. [37]</td>
<td>USA</td>
<td>0/535,000</td>
<td>Retrospective: passive surveillance</td>
</tr>
<tr>
<td>Usonis et al. [40]</td>
<td>Lithuania</td>
<td>0/4702 Jeryl Lynn or Jeryl Lynn-derived</td>
<td>Meta-analysis of eight single-blind, randomized, controlled trials: passive surveillance</td>
</tr>
</tbody>
</table>

### Table 4
Comparative immunogenicity (seroconversion) for Urabe and Jeryl Lynn mumps strains

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibody test</th>
<th>Urabe</th>
<th>Jeryl Lynn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christenson et al. [47]</td>
<td>Neut</td>
<td>60/64 (94%)</td>
<td>66/64 (91%)</td>
</tr>
<tr>
<td></td>
<td>HIG</td>
<td>66/77 (86%)</td>
<td>66/80 (63%)</td>
</tr>
<tr>
<td>Vesikari et al. [48]</td>
<td>Neut</td>
<td>76/91 (84%)</td>
<td>38/57 (67%)</td>
</tr>
<tr>
<td></td>
<td>HIG</td>
<td>67/85 (79%)</td>
<td>44/61 (72%)</td>
</tr>
<tr>
<td>Vesikari et al. [49]</td>
<td>EIA</td>
<td>90/93 (97%)</td>
<td>49/51 (96%)</td>
</tr>
<tr>
<td>Popow-Kraupp et al. [50]</td>
<td>EHI</td>
<td>190/196 (97%)</td>
<td>171/190 (90%)</td>
</tr>
<tr>
<td>Overall</td>
<td>84–97%</td>
<td>63–96%</td>
<td></td>
</tr>
</tbody>
</table>

EHI: enhanced hemagglutination; EI: ELISA; HIG: hemolysis in gel; Neut: neutralization.

### Table 5
Protective efficacy of Urabe and Jeryl Lynn strain vaccines in comparative studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Urabe Am9</th>
<th>Jeryl Lynn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popow-Kraupp et al. [50]</td>
<td>96.9%</td>
<td>90%</td>
</tr>
<tr>
<td>Nokes and Anderson [52]</td>
<td>97.9%</td>
<td>93.8%</td>
</tr>
<tr>
<td>Toscani et al. [54]</td>
<td>75.8%</td>
<td>64.7%</td>
</tr>
<tr>
<td>Chamot et al. [51]</td>
<td>73.1%</td>
<td>61.6%</td>
</tr>
<tr>
<td>Schlegel et al. [53]</td>
<td>87.0%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Canadians, which showed that 5–6 years after MMR vaccination in children 12–24 months of age, the seronegativity rates were 15% in Jeryl Lynn recipients versus 7% in Urabe recipients [57].

8. Cost

The cost difference between strains of mumps vaccine viruses used in the preparation of MMR vaccines is an important issue for national immunization programs. Higher prices for current vaccines and rising operational costs are increasing the overall cost of immunization. Information from UNICEF and PAHO indicates that the cost per dose of MMR vaccine made with the Urabe strain during 2004 was from US$1.20–1.60 compared with US$2.50 per dose of MMR vaccine made with the Jeryl Lynn strain [58–60]. In many developing nations working to finance basic immunization programs, such a cost difference can be substantial. Indeed, MMR vaccines containing the Jeryl Lynn strain do not appear in UNICEF 2004 vaccine quantities and pricing projections, and the PAHO revolving fund for vaccine prices for 2004 contains only the Urabe and Leningrad-Zagreb strain vaccines [58,60].

Although the majority of cost-effectiveness studies have been performed with the more expensive Jeryl Lynn strain, these studies have demonstrated that MMR vaccination is cost-effective [61]. Studies in industrialized countries have shown that incorporating mumps vaccines into national immunization programs is highly cost-effective. In the United States, every $1 spent on MMR vaccine saves $26 in costs associated with patient care and lost work days due to mumps [62]. The WHO has evaluated the economics of including mumps vaccine in a number of individual country settings, finding favourable benefit-cost ratios in Austria, Israel, and South Africa, indicating that adding mumps vaccine to the measles immunization program may be very cost-effective [1]. However, other studies have found that the cost of vaccine-related adverse events and the underlying health burden associated with natural mumps infection remain to be clarified and included in considerations for immunization programs in developing countries [61].

9. Positions of public health organizations

The most recent WHO position paper on mumps vaccine acknowledged that although the available data suggest that vaccines using certain strains may be associated with higher rates of aseptic meningitis, all available mumps preparations are acceptable for use in immunization programs [1]. With regard to adverse reactions to mumps vaccination, the WHO Global Advisory Committee on Vaccine Safety stated in July 2003 that higher rates of aseptic meningitis have been described for the Urabe, Leningrad-3, and L-Zagreb strain vaccines compared with the Jeryl Lynn strain vaccine. The possible virological basis for this difference and/or other characteristics of the vaccines that might explain these differences is not known [16].

In the same document, the committee noted that risk estimates for postvaccine aseptic meningitis vary among studies, reflecting differences in study settings and circumstances, and type of surveillance. They noted that available data are insufficient to distinguish between the safety profile with regard to aseptic meningitis for the Urabe, Leningrad-3, and L-Zagreb strains, and the committee was not aware of any cases of virologically proven aseptic meningitis following Jeryl Lynn vaccine. If Urabe, Leningrad-3, and L-Zagreb vaccines are being used in mass vaccination campaigns, national immunization programmes need to take into account the potential for clustering of aseptic meningitis cases following the campaigns. The committee noted that, as of 2004, all reported cases of vaccine-derived mumps meningitis have recovered. There is thus no known case of postvaccine aseptic meningitis with long-term sequelae [16].

The WHO has also stated that the data generated within the United Kingdom should not be interpreted as justifying the suspension of existing mumps immunization programs, as the incidence and severity of meningitis following natural mumps infection greatly exceeds that associated with any currently available protective vaccine [63]. As with rubella, high immunization coverage for mumps is essential because low coverage will result in an increased mean age of infection and thus potentially more severe complications. The WHO has also urged manufacturers to continue to produce Urabe strain vaccines in order to provide the quantities required by the international community [64].

Large-scale mumps vaccination is recommended in countries with an efficient childhood vaccination program and sufficient resources to maintain high-level vaccination coverage. In such countries, the combination of mumps vaccine with measles, or preferably, measles and rubella vaccines is recommended. National decisions to implement large-scale mumps vaccination should be based on careful cost-benefit analyses.

10. Conclusion

Some attenuated mumps vaccines, like mumps disease, are associated with aseptic meningitis. The lack of a standardized clinical case definition of aseptic meningitis and criteria for CSF evaluation complicates the interpretation of available data and may increase the probability of higher “case” ascertainment influenced by factors other than the vaccine strain. In addition, the rates of this complication vary according to the vaccine strain, the manufacturer, the case definition, the study design, and the intensity of surveillance. For the Urabe Am9 strain manufactured by Sanofi Pasteur for example, the variation, after primary vaccination, lies between 1 per 11,000 and 1 per 121,000 doses, which is much lower than the incidence of meningitis following natural infection. Further-
more, in evaluating the relative impact of postvaccine aseptic meningitis, it should be kept in mind that vaccine-associated aseptic meningitis typically resolves spontaneously within approximately 1 week and there are no documented long-term sequelae. It is of far greater concern that natural mumps infection may lead to encephalitis, with a high risk of death or permanent disability. Thus, countries need to consider that the incidence and severity of meningitis (which has been reported to be 1 in 400 cases) and encephalitis (estimated to occur in 0.02–0.3% of cases) following natural infection greatly exceed those associated with any protective mumps vaccine currently available on the international market [3].

Also to be considered in choosing between Urabe- and Jeryl Lynn-containing MMR vaccines are the potential strain differences in immunogenicity, efficacy, and persistence of antibody titers. As shown by a review of numerous studies, the Urabe strain is more immunogenic and effective than the Jeryl Lynn strain. According to some opinion leaders, in community-based immunization programs, the greater safety of the Jeryl Lynn vaccine is offset by the greater efficacy of the Urabe Am9 vaccine [50].

Finally, the WHO recognizes that the decision to implement large-scale national immunization programs that include mumps vaccination should be based on careful cost-benefit analyses [1]. A cost-benefit analysis of a vaccine strain should, therefore, take into account the disease burden of mumps, the efficacy and adverse event profile of the vaccine, the cost of the vaccine, and the operational costs of the prevention program and should include a comparative analysis of the costs of mumps control versus control of other prevalent vaccine-preventable diseases in the country. Different countries have made different judgments regarding the use of Jeryl Lynn or Urabe strain vaccines for the prevention of mumps, and the WHO considers all strains except Rubini to be acceptable [1].

As discussed in this paper, multiple parameters need to be considered by public health authorities when deciding which vaccine should be chosen for mumps vaccination programs. Each of the available strains has advantages and disadvantages. We conclude that the risk-benefit ratio of the Urabe, Leningrad-Zagreb and Jeryl Lynn strains is highly favourable to vaccination.

References


for Vaccine


