Mumps Outbreaks in Canada and the United States: Time for New Thinking on Mumps Vaccines

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(See the editorial commentary by Brunell on pages 467–9)

Mumps epidemics in Canada and the United States prompted us to review evidence for the effectiveness of 5 different vaccine strains. Early trials with the Jeryl Lynn vaccine strain demonstrated an efficacy of ~95%, but in epidemic conditions, the effectiveness has been as low as 62%; this is still considerably better than the effectiveness of another safe strain, Rubini (which has an effectiveness of close to 0% in epidemic conditions). The Urabe vaccine strain has an effectiveness of 54%–87% but is prone to cause aseptic meningitis. Little epidemiological information is available for other vaccines. The Leningrad-Zagreb vaccine strain, which is widely used in developing countries and costs a fraction of what vaccines cost in the developed world, seems to have encouraging results; in 1 study, the effectiveness of this vaccine exceeded 95%. Aseptic meningitis has also been reported in association with this vaccine, but the benign nature of the associated meningitis was shown recently in Croatia. Also, the Leningrad-3 strain seems to be effective but causes less-benign meningitis. No mumps vaccine equals the best vaccines in quality, but the virtually complete safety of some strains may not offset their low effectiveness. Epidemiological data are pivotal in mumps, because serological testing is subject to many interpretation problems.

An outbreak of mumps occurred unexpectedly in May 2005 in Nova Scotia, Canada, followed later by an outbreak in Quebec, Canada [1] and, in September 2005, by an outbreak in Iowa [2]. Soon, other US states were affected, with commercial flights being an effective means of dispersing infection quickly. To date, at least 45 US states have reported a total of >10,000 cases associated with this outbreak [3–5]. The fact that the isolates have all been identified as genotype G strongly suggests that the epidemic is caused by only a single strain [5, 6].

The age of affected patients has ranged from 1 year to 96 years, with the majority of patients being aged 18–24 years. In many patients, complications have developed. Among 363 male patients in Iowa, 27 (8%) had cases of orchitis, and of 1254 patients involved in the epidemic, 4 (0.3%) developed encephalitis [4]. Several cases of meningitis, deafness, oophoritis, mastitis, and pancreatitis have been diagnosed in patients involved in the outbreaks. Because the manifestations and severity of disease in vaccinees do not much differ from those found in nonvaccinated populations [7, 8], vaccinees with disease have not gained much from vaccination. Among 1798 patients in the United States, only 123 (7%) were unvaccinated, 245 (14%) had received 1 dose of measles-mumps-rubella (MMR) vaccine, and 884 (49%) were vaccinated twice [3]. In the first outbreak in Canada, 9 (69%) of 13 teenagers had received 2 doses of MMR vaccine [1]. There remains little room for discussion as to whether most cases involve vaccine failure; they do.

Received 19 January 2007; accepted 4 April 2007; electronically published 10 July 2007.

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Clinical Infectious Diseases 2007; 45:459–66

1058-4838/2007/4504-0009$15.00
DOI: 10.1086/520028

The epidemic likely originates from the United Kingdom [9], where mumps has been a growing problem, with 56,000 reported cases in 2004–2005 [10]. The question now raised is why North America is experiencing the largest epidemic since 1991, when 4264 cases were reported in the United States [11]. The vaccination coverage in the United States exceeds 95% [12], and the decrease in the number of cases to <300 cases per year prompted the declaration of a national health objective to eliminate indigenous mumps by 2010 [13]. The epidemic likely postpones that goal.

MUMPS IMMUNOLOGY: A COMPLEX ISSUE

A vaccinee may remain unprotected if the primary response is insufficient (primary vaccine failure) or if immunity wanes (secondary vaccine failure). The prevailing view [14, 15] is that most mumps vaccine failures are attributable to primary vaccine failure. This view is challenged, and with good reasoning [16–19].

A statistically significant difference has not always been demonstrated [20, 21], but receiving >1 dose of vaccine seems to be beneficial in mumps [22]; in fact, receipt of 2 doses may confer up to 5 times the protection of a single dose [23]. Realizing all of the advantages of multiple dosing (such as better tracing of individuals), Finland and Sweden adopted a 2-dose policy for MMR vaccination in 1982 [24]. As a consequence, indigenous mumps was eliminated from Finland in 1996 [25]. The United States added a second MMR vaccination dose in the schedule in 1989, and Canada and the United Kingdom added a second dose in 1996 [1, 26]. The virtual disappearance of mumps in Scandinavia and elsewhere implies that many children and young adults there are protected solely by vaccination. The receipt of only 1 dose leaves the vaccinees in danger [27], because chances to receive natural boosters are continuously lessening. But why did many individuals in North America who received 2 doses of vaccine develop mumps?

Here, we arrive at a complex issue—the differences between different mumps vaccine strains (or, preferably, substrains) [19, 28]. The main practical problem is that, although several tests are used, no serological test reliably predicts who is at risk and who is not [22]; association between positive ELISA or other serological test results and clinical protection is especially poor in mumps vaccination. Virus neutralization is the best test available [19], but it is too laborious for routine use. The only way to try to evaluate vaccines is to scrutinize the epidemiological data obtained from "real-life" conditions. Fair judgment is difficult, because only 1 strain has undergone stringent efficacy trials in the sense that we currently require. On the other hand, useful data are available from various environments, including historical data and, in particular, data from epidemic conditions. Although prone to confounding factors, those data are likely to be informative enough to give a rather reliable overview of the current situation.

METHODS

Because we have worked in the field for many years, much data existed in our own files; however, to update the information, we searched the electronic databases from 1 July 2006 through 15 January 2007. Epidemiological and reactogenicity data on different mumps vaccines were collected, and additional information was obtained by cross references. All valuable information deriving from prospective or retrospective studies, controlled trials, or observational studies was used.

Information was retrieved regarding 5 vaccine strains: Jeryl Lynn, Urabe, Rubini, Leningrad-Zagreb (L-Zagreb), and Leningrad-3. References in the articles dealing with these vaccines offered an additional way to obtain more information. We could not trace impact data on RIT 4385, which was developed from Jeryl Lynn and is used widely as a component of 1 type of MMR vaccine.

RESULTS

Jeryl Lynn. Jeryl Lynn, the only mumps vaccine strain used in the United States, is derived from a patient's throat isolate [29]. It contains 2 viral populations, which is probably an advantage. The strain is very safe, as shown in extensive reactogenicity studies using monovalent mumps [30] or combined MMR vaccine [31]. Aseptic meningitis, the Achilles' heel of mumps vaccines (vide infra), has never been documented to be caused by Jeryl Lynn [32] (albeit, in 1 case in Germany, it was claimed to have done so [33, 34]). Long-term follow-up studies with Jeryl Lynn–containing MMR vaccine [35–37] confirm the general safety of that vaccine.

Developed in 1967, Jeryl Lynn had the privilege of being the first mumps vaccine available to the international market. A randomized trial, conducted in Philadelphia, Pennsylvania, from 1965 through 1967, involved nursery school or kindergarten attendees [38]. A 20-month follow-up of seronegative children showed a 95% effectiveness (95% CI, 88%–98%), with the point estimates varying from 92% to 96%, depending on the subgroup (families vs. classrooms) or the interval from vaccination to exposure (0–10 months vs. 11–20 months). In a subsequent double-blind, placebo-controlled study among first- and second-graders in North Carolina, 5 cases were identified among 2965 vaccinees, compared with 13 cases identified among 316 control subjects, during the 180 days after vaccination [39]. The vaccine efficacy was 96% (95% CI, 88%–99%).

These encouraging results predicted good effectiveness in routine use, as well. However, vaccine failures soon occurred [40], although they were rare. A 99% reduction in reported cases occurred in the United States by 1993 [41], and the impact has been spectacular elsewhere, as well [42]. By using Jeryl

Lynn–containing MMR vaccine almost exclusively, Finland eliminated indigenous mumps in 1996 [25].

Outbreak conditions, in which the time interval from vaccination to the outbreak has varied, have brought less favorable information (figure 1). The highest efficacy, 91% (95% CI, 77%–93%), was reported from New Jersey in 1983 [52], whereas, in Geneva, Switzerland, during the period 1993–1996, it was no greater than 62% (95% CI, 0%–85%) [47]. A case-control study from British Columbia, Canada, in 1997 estimated an 80% effectiveness (95% CI, 29%–96%) [43]. Although acknowledging problems in methodology in these observational studies, one may fairly conclude that protection has not been perfect.

Rubini. Another very safe mumps vaccine derived its name, Rubini, from the Swiss child whose urine was used as the source of virus isolation [53]. The problem with this human diploid cell strain is that it has very low or no clinical effectiveness, the lower extreme being −55% (95% CI ,−122 to −9), reported in Singapore (figure 1) [46]. This is surprising, because Rubini-containing MMR causes seroconversion against mumps in 95% of children aged 14–24 months [55]. Portugal began to use this vaccine exclusively in 1992, and the country was soon swept by a large mumps epidemic [56]. Similar experiences, reported in countries such as Switzerland [57], Italy [58], and Singapore [46], have led to the abandonment of the Rubini strain [46, 57].

Urabe. The Urabe strain derives from a patient's saliva isolate. The vaccine was developed in Japan, but large quantities have been also been produced in Europe. The strain is highly immunogenic, with 95% of children aged 14–20 months experiencing seroconversion [59]. Compared with the Jeryl Lynn vaccine, the immunogenicity of the Urabe vaccine, measured by ELISA (whatever that might mean in terms of protection), is at least equivalent. More importantly, 88% of children aged 13–15 months who receive the vaccine develop neutralizing antibodies [60].

The problem with the Urabe vaccine is that it is prone to cause aseptic meningitis [61]. The reason for this is not entirely clear, but the vaccine contains 2 distinct strains, 1 of which seems to be more neurovirulent [62]. Meningitis occurring after administration of mumps vaccine is clinically very mild, but understandably, any vaccine-induced inflammation of the CNS is a matter of concern. The incidence rates vary from as high as 1 case per 900 doses in 1 prefecture of Japan [63] to 1 case per 62,000 doses in Canada [64] and 1 case per 120,000 doses in France [65]. Such great differences in incidence are partly dependent on the manufacturer of the vaccine.

In clinical effectiveness, the Urabe vaccine competes with the

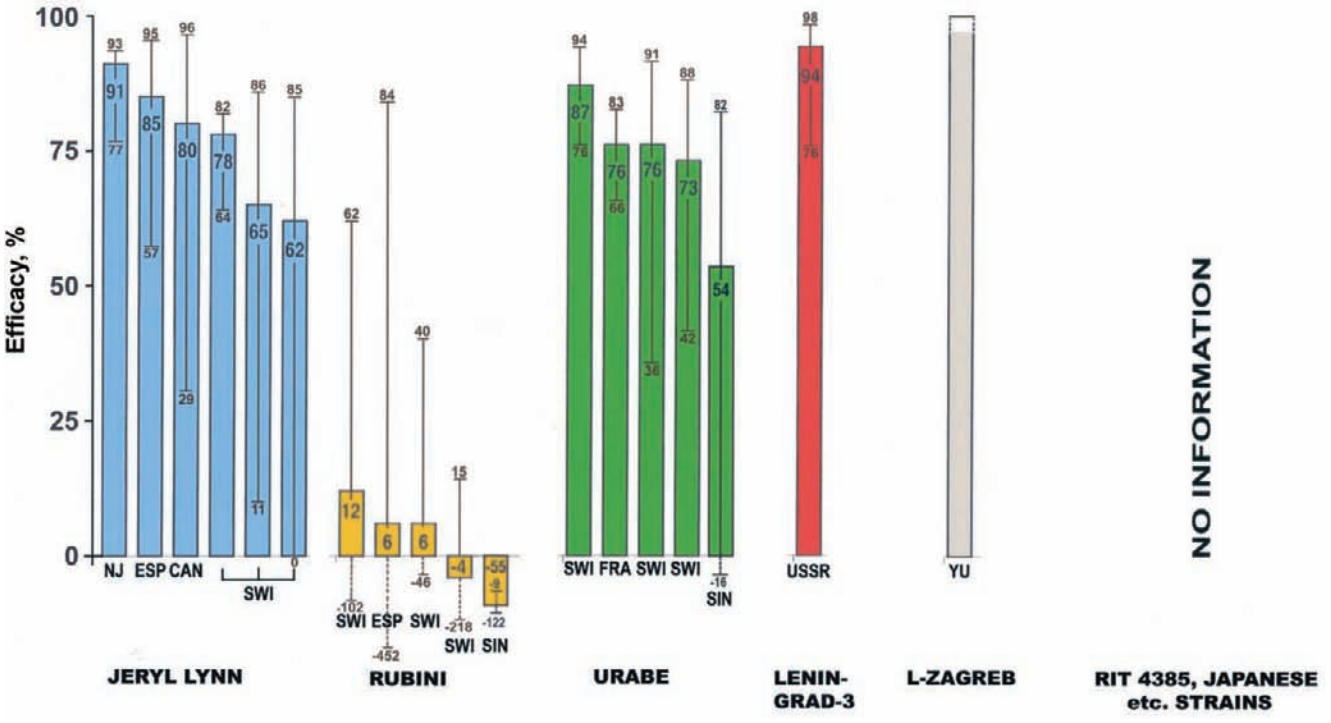

Figure 1. Clinical efficacy in outbreak conditions of 5 mumps vaccine strains reported in representative studies. Brackets indicate 95% CIs. CAN, Canada [43]; ESP, Spain [44]; FRA, France [45]; NJ, New Jersey [40]; SIN, Singapore [46]; SWI, Switzerland [21, 47]; USSR, former Union of Soviet Socialist Republics [48]; YU, former Yugoslavia [49–51].

Jeryl Lynn vaccine. In outbreak conditions, an effectiveness of ~75% [21, 47, 45] has been observed (figure 1), the extremes being a high of 87% (95% CI, 76%–94%) in a Swiss study [54] and a low of 54% (95% CI, −16% to 82%) in Singapore [46].

Leningrad-3. Researchers of the former Soviet Union developed the Leningrad-3 vaccine in the 1960s, and Russia has used it since 1981 [66]. The vaccine was prepared in a guinea pig kidney cell culture and passaged in Japanese quail embryo cultures [49]. It was tested in a small series of children aged 3–6 years [48]. Because mumps developed in 2 (2%) of 85 vaccinees, compared with 42 (39%) of 108 nonvaccinees, the effectiveness was calculated as 94% (95% CI, 76%–98%). Subsequent studies have suggested a protection of 91%–99% [67].

Unfortunately, aseptic meningitis is a particularly common event among recipients of the Leningrad-3 strain vaccine, and clinical trials were cancelled because of this problem in the former German Democratic Republic [68]. As was shown recently in Novosibirsk, Siberia [69], the Leningrad-3 strain may also transmit horizontally and cause symptomatic disease in vaccinees. For these reasons, Leningrad-3 vaccine has not gained much attention outside of the countries of the former Communist bloc.

L-Zagreb. Brought to Zagreb, Croatia (in the former Yugoslavia), the Leningrad-3 vaccine was further attenuated and was renamed L-Zagreb. It meets the World Health Organization requirements and has been sold in tens of millions of doses, especially in the developing world. Early immunogenicity studies involving 6800 preschool children, conducted in 1971, showed a rate of seroconversion by hemagglutination inhibition of 88%–94% [66]. The rate of adverse reactions did not differ from that found in the control group.

From the Balkan peninsula, data has been reported on the impact of the L-Zagreb vaccine in nonepidemic conditions. L-Zagreb–containing MMR vaccination became compulsory in Croatia in 1976, and reported mumps cases decreased by >90% [50]. In Slovenia, a 2-dose program has maintained a coverage rate of >90% since 1990, and the incidence of mumps has remained at 2 cases per 100,000 vaccine doses [42]. Because the reporting of infectious diseases in the former Communist block used to be fairly reliable, there should be few flaws in this information.

For the vaccine's performance under epidemic conditions, we have more-solid data. In an outbreak that occurred in Yugoslavia in 1976, a total of 164 (7%) of 2434 nonvaccinated first-graders developed mumps, whereas no cases were found among 696 individuals who had received L-Zagreb–containing MMR vaccine. Assuming a case in 1 (0.1%) of these 696 children and similar exposure in these 2 populations, the effectiveness might have been ⩾97% [49]. Effectiveness of 97%–100% was also reported among preschool children [50]. In a kindergarten setting, no cases of mumps were detected among 40 vaccinees, compared with cases in 74 (38%) of 197 nonvaccinees [51]. Compulsory vaccination with obligatory reporting began in the Rijeka region of Croatia in 1976 [70]. Epidemics with a peak incidence of 552 cases per 100,000 doses per year occurred in 1977 and during 1981–1982; thereafter, the incidence of mumps remained at 31–78 cases per 100,000 doses for at least 8 years [70]. Simultaneously, a shift in age distribution occurred from children aged 5–9 years to adolescents. Both observations speak for the effectiveness of vaccination.

Five municipalities of Brazil performed a large-scale mumps vaccination campaign with L-Zagreb–containing MMR vaccine in 1997. A total of 105,098 doses were administered to children aged 1–11 years, and the vaccine coverage was 95% [71]. Comparing the 2.5 years before the campaign with the 3 years after the campaign, the number of reported cases of mumps-related meningitis decreased from 16 cases to 0 cases. The crude annual rate of mumps decreased by 93% (95% CI, 86%–96%).

An association with aseptic meningitis has also been a matter of concern with the L-Zagreb strain. The discussion began in Brazil, where, in 1998, an observation was made that, following 2 mass campaigns using MMR vaccine, a high incidence of aseptic meningitis was found [71, 72]. The estimates varied, but within 3 weeks after vaccination, the rate of aseptic meningitis ranged from 1 case per 6199 doses (95% CI, 4854–8058 doses) to 1 case per 19,247 doses (95% CI, 12,648–29,513 doses), depending on the diagnostic criteria used and the state of Brazil that the data were from.

The interpretation of the Brazilian data has been challenged [73]. A retrospective study from India found only 1 case of aseptic meningitis per 95,361 doses (95% CI, 0.5–1.6 cases per 100,000 doses) [74], and an incidence of 0.96 cases per 100,000 doses was estimated in the Bahamas [75]. No mumps or mumps vaccine viruses were identified in these surveys. Instead, viruses were searched for using samples of CSF from 50 patients with cases of meningitis following L-Zagreb vaccination in Croatia during the period 1988–1992 [76]. All cultures showed no growth, except 1 case in which Coxsackie virus B4 was detected. In a similar setting in Brazil, 8 patients with cases of meningitis were checked for the presence of virus in 1998 [77]; all patients had negative results. A recent study from Croatia [78] suggests that primary L-Zagreb vaccination may cause aseptic meningitis at the rate of 1 case per 2020 vaccinees, but methodological problems [79] might have led to a gross overestimation of this rate. Of special note, the clinical disease was benign, all patients were discharged from the hospital in good condition, and no neurological symptoms were detected during a 36-month follow-up period [78].

To disclose the true incidence of aseptic meningitis following vaccination with the L-Zagreb strain, a massive prospective study was undertaken among >300,000 children in Egypt. The

study was funded by the Indian manufacturer of the vaccine (Serum Institute of India) [80]. Results are yet to be published, but not a single case of aseptic meningitis was detected (Saeed Aly Oun, personal communication). This information adds to the view that aseptic meningitis is not a major issue with respect to vaccination with the L-Zagreb strain, especially if weighed against the good protection provided by the vaccine against overt mumps and its associated complications.

Other strains. Several other strains have been used for mumps vaccination, but mostly in only a single country or area. In Japan, strains such as Hoshino, Miyahara, Torii, and NK M-46 have been produced. Iran has its own strain, called S-12, which is produced on human diploid cells (as is the case with Rubini) [81]. Common to all of these vaccines is the fact that little information is available on their clinical effectiveness (which may be good). Bulgaria produced a strain named Sofia-6 in guinea pig kidney cell culture. The vaccine was introduced into the Bulgarian national vaccination program in 1977, and targeted vaccination for children aged 4–12 years was executed in 1982. The effectiveness was reported to be good [82], but the vaccine was prone to cause adverse events, including aseptic meningitis, which led to its abandonment.

The predecessor of the European consortium GlaxoSmithKline developed a vaccine strain called RIT 4385 from the Jeryl Lynn strain by leaving out 1 of the 2 virus populations and adding further passages. The clinical effectiveness of this vaccine strain has not, thus far, been determined. Safety is not a problem, as shown by a large passive surveillance study of RIT 4385–containing MMR vaccine in Germany [83].

DISCUSSION

Where are we now with respect to mumps vaccines? To unwind the tangled skein of the data on mumps vaccination is a challenge. Which vaccine to recommend? Although the World Health Organization deems all vaccine strains except Rubini to be acceptable [84], there is more than a single answer. Experience obtained from outbreaks (figure 1) suggests that vaccine effectiveness is lower than one would expect from the findings of serological studies (which are unreliable) or controlled efficacy trials (of which there are only a few). Waning immunity has not been deemed to be important [14, 15, 85, 86], but outbreaks in highly vaccinated populations [1, 2, 14–16, 18–20] warrant some rethinking. Also, modeling of the serological information [19, 27] supports the view that waning immunity is an issue. We recommend that IgG avidity measurement, which works so well in the context of measles vaccination [87–89], be used as an important tool when addressing the difficult question of whether a mumps vaccine failure is primary or secondary. With avidity testing, Japanese investigators found that secondary vaccine failures occurred even in school children, whose exposure to wild mumps was likely to be high (a population with low vaccine coverage) [90]. Obviously, avidity testing has the potential to increase our understanding of the true role of waning immunity after mumps vaccination.

Immunological data on mumps vaccination are abundant, but as vaccine trials indicate [55, 59], the interpretation problems are immense. The immunogenicity of the Jeryl Lynn– and RIT 4385–containing MMR vaccines was examined in a double-blind study involving German children [91] that used neutralizing antibodies as a yardstick (the best method available) [19]. Seroconversion against the vaccine strains occurred in 96% and 91% of the children, respectively, but seroconversion against wild mumps virus occurred in only 75% and 68%, respectively. Because usually only antibodies against the vaccine strain are measured, good results can be obtained that do not reflect the actual ability of the vaccine to provide protection from disease. A vaccine failure is investigated properly only if, in addition to avidity testing [87–90], the ability of antibodies to neutralize wild mumps virus has been checked.

A mathematical model assessing the potential of vaccination using the Urabe or Jeryl Lynn strains [92] suggested that, in community-based programs, the greater apparent safety (i.e., fewer vaccine-induced complications) associated with the Jeryl Lynn strain is offset by the potentially greater effectiveness associated with the Urabe strain (i.e., fewer complications caused by wild mumps virus). Thus, it may not always be in the interest of the community to use the vaccine associated with the lowest rate of complications. Vaccines that use the Jeryl Lynn and Rubini strains are documented to be very safe vaccines, but once vaccine failure has occurred, the rate of complications in vaccinees is not very different from the rate of complications in nonvaccinees. The exact incidence of aseptic meningitis associated with natural mumps is not known, and it probably varies in different settings; a conservative estimate is 1 case of aseptic meningitis per 400 cases of clinical mumps [93]. In a well-studied prevaccination epidemic in Denmark, the CNS was affected in no less than 65% of cases [94]. These figures (or whatever the actual figure is), which apply to nonbenign aseptic meningitis caused by natural mumps, must be weighed against the figures for vaccine-induced meningitis, which is considerably milder [78] and develops with a much lower frequency. The time has arrived to put things in perspective [92, 95].

In the field of immunization, we are spoiled by having several virtually harmless but very effective vaccines (e.g., inactivated polio vaccine and *Haemophilus influenzae* type b vaccine). Current mumps vaccines do not equal those, but they are still of great potential. Money should not be the only decisive factor, but it allows one to rank vaccines in certain order: a single-dose vial (according to the price for the US-manufactured vaccine) costs $.90, $1.20, and $2.50 for MMR vaccine containing L-Zagreb, Urabe, and Jeryl Lynn strains, respectively [96, 97]. If an effective vaccine is generally (although not completely)

safe but costs much less than a slightly better tolerated but not necessarily more effective vaccine, money becomes an issue. Research is urgently warranted to better characterize the pros and cons of vaccine strains now shadowed by strongly advertised, highly priced competitors.

Acknowledgments

Potential conflicts of interest. P.S.K., S.V.K., S.S.J., and R.M.D. are employees of Serum Institute of India (Pune, India), which is the manufacturer of a measles-mumps-rubella vaccine containing the Leningrad-Zagreb strain. H.P. serves as a scientific consultant for the Serum Institute. M.P. is employed by World Bank (Washington, DC).

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