

REVIEW



## Close the gap for routine mumps vaccination in Japan

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### ABSTRACT

Mumps is a vaccine-preventable disease. Because the mumps vaccine can cause aseptic meningitis in rare cases, this vaccine is not routine in Japan. This has led to low vaccine coverage and severe disease burden in Japan. The present review summarizes mumps epidemiology and vaccination and discusses effective future strategies to mitigate the current disease burden of mumps in Japan. Although a recent study reported that mumps vaccine coverage rates are improving in Japan, current coverage rates are far below the optimal rate to suppress the ongoing epidemic, which has caused an average annual financial loss of 85 billion JPY between 2000 and 2016. Recent reports have demonstrated a much lower incidence of vaccine-induced aseptic meningitis in newly developed vaccines, especially when administered at 1 year of age. Cost-effectiveness studies suggest that routinization of the currently distributed domestic vaccine would be highly cost-effective. In addition, questionnaire surveillance data suggest that the majority of the Japanese population accepts the nominal risk of the vaccine when the proper information is provided. Finally, there are some successful programs in Japan that have attained high vaccine coverage rates with financial support from local governments. Taken together, these data suggest that the mumps vaccine should be immediately included in routine vaccines in Japan.

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### Introduction

Mumps is a vaccine-preventable disease. Classic mumps illness is characterized by fever and swelling of the parotid glands and affects both children and adults. Serious complications after mumps infections are relatively common and include aseptic meningitis 1%–10%, encephalitis 0.03%–0.2%, hearing loss 0.1%, orchitis 25% in adult men, and oophoritis 5% in adult women.<sup>1</sup> Vaccination is the most effective and established method to prevent mumps illness. In most countries, two-dose mumps vaccines are included in national immunization programs (NIP). In these countries, the government generally covers the cost of mumps vaccines.

In Japan's NIP, vaccinations are divided into two categories, routine and voluntary vaccinations. In routine vaccinations, the vaccine cost is covered by national and local governments, and Japanese children are recommended to receive these routine vaccines. For voluntary vaccines, families are required to pay the vaccine cost out-of-pocket, and no governmental financial support is available.<sup>2</sup>

A Japanese strain of the measles-mumps-rubella (MMR) vaccine (Urabe AM9) was introduced in Japan and was included in routine vaccinations of the 1989 NIP.<sup>3</sup> However, because of aseptic meningitis due to the vaccine (up to approximately 1/900), the Japanese Ministry of Health, Labor and Welfare (MHLW) excluded it from the routine vaccines in 1993.<sup>4,5</sup> Subsequently, measles and rubella vaccines have been recommended for children over 1 year of age as routine vaccinations in the NIP, but the monovalent

mumps vaccine has been a voluntary vaccination, which has led to low mumps vaccine coverage and severe disease burdens in Japan over the past 25 years. Unfortunately, the Japanese government has thus far been unable to resume universal mumps vaccination, despite explicit warnings from Japanese and foreign public health officials.<sup>6,7</sup>

The present review summarizes mumps epidemiology and vaccination and evaluates effective future strategies to mitigate the current mumps disease burden in Japan. This review also seeks to inform health-care professionals, patients, and the general population of the importance of routine mumps vaccination.

### Global mumps epidemiology and vaccination

Mumps is a moderately to highly contagious disease with a basic reproductive number between 4 and 10.<sup>8,9</sup> Before the mumps vaccine was introduced, mumps pandemics occurred approximately every 4–5 years, and mumps was a leading global cause of viral encephalitis, meningitis, and hearing loss.<sup>10,11</sup> In the pre-vaccination era in Europe from 1977 to 1985, average incidences were reported as approximately 290 cases/100,000 person-years.<sup>1</sup> Partly because some patients are asymptomatic or develop very mild symptoms, substantial under-reporting is likely, which was demonstrated by a survey from the US.<sup>12</sup> In unvaccinated populations, almost all persons develop the infection prior to adolescence, with 90% of children aged 14–15 years presenting as seropositive.<sup>1</sup>

By the end of 2018, mumps vaccines had been introduced nationwide in 122 countries.<sup>13</sup> In countries where vaccination has been introduced with high coverage rates, the incidence of mumps has dropped dramatically. Galazka et al. identified that in countries in which two-dose routine vaccination was introduced, mumps infection rates dropped 97–99.9% after routinization.<sup>1</sup> For example, Finland achieved more than a 99.9% reduction in cases by introducing a two-dose vaccination program, and Germany estimated that the incidence of mumps in the post-vaccination period was reduced to 10.3/100,000 persons.<sup>14,15</sup>

In terms of herd immunity, considering that the basic reproductive number of mumps is between 4 and 10, more than 75–90% of the population should be immune to mumps to suppress endemics.<sup>8,9</sup> Because a single dose of mumps vaccine does not confer immunity in all recipients, a two-dose vaccine program is recommended. However, countries that have attained high-coverage two-dose vaccine regimens sporadically experience mumps epidemics, primarily in the adolescent or adult population due to waning immunity after years of vaccination. In these countries, a third administration of the vaccine has been discussed.<sup>16,17</sup>

The mumps vaccine is often neglected, especially in developing countries due to the lack of accurate disease burden estimates in these countries.<sup>18–20</sup> The main countries in which routine mumps vaccination has not yet been introduced are some African countries and some Asian countries, including Japan.<sup>13</sup> In countries where routine vaccination has not yet been introduced, the incidence of mumps remains high, mostly affecting children aged 5–9 years.<sup>1,13,18–20</sup>

## Mumps epidemiology and vaccination in Japan

Before the introduction of mumps vaccine, Japan had experienced mumps epidemic every 4–5 years based on national surveillance reported by the National Institute of Infectious Diseases.<sup>21</sup> For epidemiological surveillance, mumps has been monitored by a sentinel reporting system rather than a census report. Therefore, the exact incidence of mumps illness in Japan is not known, but 25–100 patients per designated health-care facility had annually been reported in pre-vaccine era in Japan, and the majority of infected population was preschool and school-aged children (children aged 1–4 and 5–9 accounted for 48% and 42% of total mumps infections in 1983).<sup>21</sup> A previous study published in the pre-vaccine era reported that mumps accounted for approximately 50% of pediatric total deafness.<sup>22</sup> After the introduction of routine

mumps vaccination, the incidence of mumps had significantly decreased to 14.00 patients per designated health-care facility in 1991. However, since the withdrawal of the mumps vaccine from the routine NIP in 1993, the vaccine coverage rate has been very low in Japan. A questionnaire study in 2005 revealed that only 23.2% of parents reported that their children had received at least one dose of mumps vaccine.<sup>23</sup> A recent study in Tokyo revealed that mumps vaccination rates confirmed by documents in 2012, 2014, and 2016 were 27.6%, 59.5%, and 61.8%, respectively.<sup>24</sup> A subsequent questionnaire survey from Nara in 2017 revealed that coverage rates reported by parents were 53.0% for one dose and 15.1% for two doses, although this study was based on parental reporting rather than official documentation, which could have falsely inflated the estimated coverage rate.<sup>25</sup> Although recent reported coverage rates have improved, these are far below the optimal coverage rates to suppress the ongoing mumps epidemic in Japan.

Suboptimal vaccine coverage has caused tremendous mumps incidence, and mumps is a major disease burden in Japan. It is estimated that 400,000 to 1.5 million patients are infected with mumps annually in Japan between 2000 and 2016.<sup>26</sup> Japan recently experienced another mumps epidemic in 2016.<sup>22</sup>

Due to the ongoing uncontrolled infection in Japan, mumps-induced sensorineural hearing loss remains a major cause of acquired hearing loss, accounting for up to 25% of pediatric single-sided deafness.<sup>27</sup> Unfortunately, a recent national survey revealed at least 348 cases of new-onset hearing loss due to mumps infections in 2015–2016, the majority of which were not reversible.<sup>7</sup> Another study identified that only 1.5% of cases with severe hearing loss due to mumps infection completely recovered.<sup>28</sup>

## Vaccine strain, safety, and efficacy globally and in Japan

Different mumps vaccine strains are available worldwide, all of which are live-attenuated vaccines. The currently distributed major strains are presented in Table 1. The Jeryl Lynn strain is widely distributed in North America and Europe. Urabe AM9 is another widely distributed strain and is distributed primarily in developing countries.

The vaccine effectiveness for each strain varies by report. The effectiveness of the Jeryl Lynn strain is usually reported as 64–81% with one dose and 83–88% with two doses.<sup>30,34,38–42</sup> The effectiveness of the Urabe AM9 strain is comparable to

**Table 1.** Currently distributed major mumps vaccine strains worldwide.

Strain	Genotype	Effectiveness (one dose/two dose) [reference]	Aseptic meningitis [reference]	Distribution country
Jeryl Lynn	A	65–78/84–86 <sup>[29,30]</sup>	1/1,000,000–1/1,800,000 <sup>29,31</sup>	North America, Europe
RIT 4385 (derived from Jeryl Lynn)	A			
Urabe AM9	B	73–87/ <sup>–[29,30]</sup>	1/14,000–1/28,400 <sup>29,31</sup>	Developing countries
Leningrad-3	N		1/1,000 <sup>32,33</sup>	Russia
Leningrad-Zagreb (derived from Leningrad-3)	N		1/1,000 <sup>32,33</sup>	Croatia, Slovenia, India
S-12	H			Iran
Hoshino	B	78–90/ <sup>–34</sup>	1/2,000–1/140,000 <sup>34–37</sup>	Japan
Torii	B			Japan

the Jeryl Lynn strain, and may potentially be slightly higher (reported as 54–87% for one dose).<sup>29,30,34</sup> Strains currently distributed in Japan, the Torii (Takeda Pharmaceutical Company Limited) and Hoshino (Kitasato Institute, Research Center for Biologicals) strains, are estimated to have 78–90% effectiveness for one dose, but data for two-dose regimens are currently unavailable.<sup>34</sup>

In all vaccine strains, local reactions, low-grade fever, parotitis, and rashes are the most common adverse events. In a comparative study of the Jeryl Lynn, Urabe AM9, and Leningrad–Zagreb strains in MMR combination vaccines, the frequency of parotitis in vaccinated children was 0.5%, 1.3%, and 3.1%, respectively, compared to 0.2% in unvaccinated controls.<sup>43</sup> A study with Japanese strains reported that salivary gland swelling after vaccination was 0.16–1.8% when the vaccine was administered to 1 year old children.<sup>34,35</sup>

Aseptic meningitis is one of the most concerning adverse events of mumps vaccine. The incidences of aseptic meningitis due to the Jeryl Lynn and Urabe AM9 strains are estimated as 1/1,000,000–1/1,800,000 and 1/14,000–1/28,400, respectively.<sup>29,31</sup> The incidence of aseptic meningitis due to Leningrad-3 or Leningrad–Zagreb strains is estimated to be approximately 1/1,000.<sup>32,44</sup> Another study from the US showed Jeryl Lynn strain did not have increased risk of aseptic meningitis.<sup>33</sup> Overall, it has been shown that Jeryl Lynn strain has fewer incidence of aseptic meningitis than that of other strains.<sup>45</sup> In terms of Japanese vaccine strains, a previous study in Japan reported that the incidence of aseptic meningitis was 1.24% in patients with symptomatic natural mumps infection, and was estimated to be 0.7–1.1% of overall infected persons including asymptomatic infections, and 0.05% in vaccine recipients.<sup>36</sup> A subsequent study revealed that receiving the first vaccine dose at 1 year of age, as per the currently recommended voluntary schedule in Japan, lowered the incidence of aseptic meningitis to 1/6,443–1/783,000.<sup>34,35</sup> A recent report from Nagoya city revealed that the incidence of aseptic meningitis due to Hoshino and Torii strains was 1/140,000.<sup>37</sup>

### Cost-effectiveness of routine mumps vaccination

Cost-effectiveness studies were previously performed in developed countries, mainly during the pre-vaccine era.<sup>46,47</sup> All studies suggested that routine mumps vaccination was highly cost-effective. The major mumps vaccine cost-effectiveness studies are summarized in Table 2. An Austrian study in the

pre-vaccination era calculated that the cost-benefit ratio (CBR) of a combined measles and mumps vaccine was 4.48 from a societal perspective.<sup>46</sup> A routine second MMR dose was estimated as cost-beneficial in Canada, with a CBR of 3.25.<sup>48</sup> The present two-dose schedule of MMR vaccines in the USA was estimated to have a CBR of 14.2 for direct costs and 26.0 for societal costs, and the CBRs for mumps vaccine alone were 13.2 for direct costs and 24.9 for societal costs.<sup>49</sup> CBR is the ratio of the benefits of a project, expressed in monetary terms, divided by its costs. CBR>1 suggests that the project is cost-beneficial.

Several cost-effectiveness studies of routine mumps vaccination have been conducted in Japan. A study, which compared the current voluntary vaccination scenario with the scenario the government had switched to routine vaccination in 2007, calculated that the CBR of routine mumps vaccine was 4.33–5.70 from a societal perspective, depending on the vaccine cost and mumps diagnosis rate.<sup>50</sup> A study using the Markov model also revealed that switching to two-dose routine vaccination was more cost-effective than continuing the current voluntary vaccination, and that receiving a second dose at 3–5 years of age was the most favorable.<sup>51</sup> A 2017 study using a static model also indicated that, if the government had switched to a routine vaccination instead of the current voluntary vaccination, the societal CBRs were 3.69 and 6.84 in independent inoculation and simultaneous inoculation, respectively.<sup>52</sup> This cost-effectiveness study estimated the average annual medical cost of mumps illness was 21.6 billion JPY, and the average annual social cost was 63.3 billion JPY, in addition to 9,487 JPY in average annual quality-adjusted life years (QALY) loss between 2000 and 2016. The most recent cost-effectiveness study in 2018 using the dynamic transmission model suggested that over the next 50 years, routine mumps immunization would save a total of 860 billion JPY and 184,779 QALYs compared to the current vaccination program.<sup>53</sup> All Japanese cost-effectiveness studies suggested that routine mumps immunization would be highly cost-effective.

### Acceptance in the general population and local mumps vaccine projects in Japan

A few studies have reported vaccine acceptance in the Japanese general population. A 2012 study in the Fukushima prefecture revealed that 70.7% of parents wanted their

**Table 2.** Cost-effectiveness studies of mumps vaccination.

Country (year) [reference]	Analyzed component	Model	Results of routine mumps vaccination
Austria (1979) <sup>46</sup>	Measles/mumps	Static	CBR 4.46 for society
USA (1982) <sup>47</sup>	Mumps	Static	CBR 7.4–39
Canada (1997) <sup>48</sup>	MMR (2nd dose)	Static	CBR 3.25 for society
USA (2004) <sup>49</sup>	MMR	Static (decision tree)	CBR 26.0 in MMR and 24.9 in mumps for society
Japan (2007) <sup>50</sup>	Mumps	Static	CBR 4.33–5.70 for society
Japan (2014) <sup>51</sup>	Mumps	Static (Markov model)	Cost-effective (2nd dose at 3–5 years was the most favorable)
Japan (2017) <sup>52</sup>	Mumps	Static	CBR 6.84 for society
Japan (2018) <sup>53</sup>	Mumps	Dynamic	Cost-effective (dominant)

CBR: cost-benefit ratio. CBR>1 suggests that the mumps vaccine is cost-beneficial

MMR: measles-mumps-rubella

All studies in Japan were based on data from domestic mumps vaccine strains.

Cost-effective means that the incremental cost/incremental quality-adjusted life years is below 1–3 times of gross domestic product per capita.

Dominant means mumps vaccine is cost-saving and increases quality-adjusted life years.

children to receive a mumps vaccination before the provision of vaccine information, while 86.3% of parents desired the vaccine after reading the vaccine information.<sup>54</sup> A 2017 study in the Nara prefecture revealed that 95.0% of parents desired routine mumps vaccination after the provision of proper vaccine information, including effectiveness and adverse events of currently available domestic strains.<sup>25</sup> This study also illustrated that even if parents were provided with proper information regarding the mumps vaccine, only 61.7% of parents planned to vaccinate their children without routine vaccination, which would require out-of-pocket payment for the vaccine. Contrastingly, 92.1% of parents desired the vaccine under a proposed routine vaccine schedule, in which the government would pay the vaccine cost. The vaccine cost is approximately 6,000 JPY per dose.<sup>50–53</sup>

Some local governments offer financial support for the cost of mumps vaccines. The coverage rate in 1-year-old children increased from 24.3% prior to partial financial support from the local government to 91.0% in 2016 after 7 years of the support program in Nagoya city. Kameyama city also attained a coverage rate of 74.4% from 2008 to 2012 with partial financial support.<sup>34,37</sup>

These studies revealed that the majority of the Japanese population desires the currently available domestic vaccine strains if provided with the proper information. However, high coverage rate cannot be achieved without routinization and government support of the vaccine.

### Policy concerns for vaccination in Japan

Japanese governments have hesitated to resume routine mumps vaccination due to the concern of vaccine-induced aseptic meningitis. The Ministry of Health, Labor and Welfare deferred the routinization of the mumps vaccine until a new, safer vaccine is developed.<sup>55</sup> However, the current mumps disease burden is much larger, with tremendous financial deficits compared to that of adverse events due to the vaccination, as demonstrated by the above cost-effectiveness studies. Further, recently reported vaccine safety data identified a much lower incidence of aseptic meningitis than that of the 1990 s.<sup>34–37</sup> Unfortunately, no new vaccine is expected to be approved in Japan as of December 2019, and none of the vaccines currently under development are superior to currently available vaccines, although some trials for novel vaccine strains have been reported globally.<sup>56,57</sup>

Although “vaccine gap” between the vaccine policies of Japan and other developed countries has diminished over the past few decades, the Japanese government has not yet been able to advocate some beneficial vaccines, including mumps vaccine, due to concerns of adverse events.<sup>58–60</sup> Because the benefits of these vaccines are much greater than the risk, the government is encouraged to support and recommend these vaccines<sup>[58–60]</sup>. If the safety of domestic strains is still a concern for the government, replacing with Jeryl Lynn strain to resume routine mumps vaccination should be considered immediately.

### Future directions

The disease burden of mumps in Japan is substantial, and no novel vaccine strain is likely to be approved in the next few years in Japan. Therefore, immediately introducing routine vaccines with currently distributed domestic strains is suggested as the best course of action. Importing international vaccine strains, such as the Jeryl Lynn strain, for routine vaccination is one potential option, but the approval process for non-domestic strains could require several years. Due to the excellent acceptance rate of the general population, cost-effectiveness studies, recent safety profiles, and successful local programs, routine nationwide vaccination should be considered. Vaccine promotion to the general population is very important. However, there is evidence that promotion without financial support will fail to achieve the optimal coverage rate. Once the routine vaccination program is initiated, health-care providers are encouraged to explain the nominal risk of aseptic meningitis, but also that the benefit is expected to be much larger than the risk to promote vaccine acceptance. Additionally, disease incidence and adverse events should be continuously monitored.

### Conclusion

Mumps remains a major epidemic disease and causes a significant disease burden in countries where the vaccine is not yet routine. Mumps vaccine has been neglected, and routinization of the vaccine has been deferred in Japan. However, all data for the mumps vaccine suggest that it should be immediately included as a routine vaccine in Japan.

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