Long-term epidemiologic longitudinal study on the effect of vaccines on public inoculation

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Public vaccination policies in Japan for several viruses have achieved favorable results. To accurately evaluate their overall effectiveness, we conducted a 45-year epidemiological survey of measles, varicella and mumps cases at our clinic. The number of patients with measles was found to be significantly decreased with the single-dose vaccination provided at public expense. However, we also witnessed an increasing trend of infection at a later age. The vaccination rates for varicella and mumps were relatively low because of their optional availability in Japan, and thus they cannot be considered to confer public protection. Although localized to a particular region, our results show that it is important to increase the immunization rate of vaccines for large-scale protection against viral infections through public programs.

Key words: vaccines, measles, varicella, mumps.

Due to their potent infectivity, measles, varicella and mumps have long been regarded as representative infectious diseases during childhood. In Japan, they are designated as school-based infectious diseases[1]. The severity of clinical symptoms depends on age, health condition, nutrition, and environment, and severe complications, such as disorders of the central nervous system, aseptic meningitis and encephalitis, and hearing impairment can occur. Therefore, vaccination for such viruses plays an important role in their prevention and in overall public health. In Europe and the United States, two-dose inoculation with the measles-mumps-rubella vaccine (MMR) is recommended[2,3]. Inoculation systems for varicella vary among countries[4]. In Japan, a measles vaccine has been provided at public expense over the past 30 years, but inoculation with varicella and mumps vaccines is voluntary, i.e., individuals must pay for these themselves.

In this study, we investigated the effect of such vaccines on incidence and age based on a 45-year epidemiological observation of viral infectious diseases at our clinic.

Material and Methods

Patients

Patients with measles, varicella, mumps, herpangina, or exanthema subitum, from among the children with general illness who presented to our medical office, were intended for analysis.

Calculation of the incidences of measles, varicella, mumps, herpangina, and exanthema subitum

The diagnosis of viral infections was based on clinical findings with or without epidemiologic findings. In the absence of an apparent outbreak of measles, varicella or mumps, a diagnosis was made using laboratory findings in addition to clinical findings.

We calculated the incidences of measles, varicella and mumps based on weekly reports accumulated between 1964 and 2008 at our outpatient clinic, including those published from 1981 to 2008 though our designation as a central health institution of Matsumoto City for the "Infectious Disease Surveillance" study

conducted by the Ministry of Health, Labor and Welfare of Japan. We also included monthly reports on infectious diseases submitted from 1996 to 2006 by local elementary and junior high schools. In May 2007, we surveyed the rate of preventive vaccination and incidence of infectious disease among children aged 3-5 years in two kindergartens in Matsumoto city; responses were obtained from parents in 525 (91.3%) of 572 children,. We referred to the rate of preventive vaccination recorded at three-year-old health screenings in Toda city in Saitama, Japan, as well.

To evaluate the effectiveness of preventive vaccination on large-scale protection, we compared the number of patients who suffered from the viral infections before and after vaccination. We classified the survey period into four groups: Group A, 1970 to 1974; Group B, 1982 to 1986; Group C, 1996 to 2000; and Group D, 2001 to 2005.

The number of residents aged from 0 to 14 years in Matsumoto city rose until 1980 (42,651, 46,832, and 47,022 in 1970, 1975, and 1980, respectively). Thereafter, this age range decreased (44,014, 38,497, 35,463, 34,240, and 33,168 in 1985, 1990, 1995, 2000, and 2005, respectively).

In Groups A, B, and C, we calculated the modified number of patients by multiplying the total number of patients with each type of viral infection over five years by a modification coefficient, which was calculated as: modification coefficient (Groups A, B, and C) = (total number of outpatients who consulted our clinic, including those with any of the five infectious diseases in Group D) ÷ (total number of outpatients who consulted our clinic in Groups A, B, or C). Children referred to our clinic twice or more were registered as one patient. Coefficients were 0.72 (20,880 ÷ 29,000) for Group A, 0.62 (20,880 ÷ 33,677) for Group B, 0.90 (20,880 ÷ 23,282) for Group C, and 1.0 for Group D. Age at onset was divided into four groups as: 0-4, 5-9, 10-14, and 15 years or older.

Statistical Analysis

We employed the chi-square test for all statistical comparisons. The level of significance was defined as a p value of less than 0.05.

Results

1) Measles

In Japan, voluntary inoculation with live, attenuated vaccine was initiated in 1969 and continued until 1977. The vaccination rate was approximately 30% during that time. Measles vaccination at public expense for children aged from 12-89 months was started in 1978, and was switched to MMR in April 1989. In 1994, the measles vaccine was re-employed alone to inoculate children aged 12-24 months. In Toda city, the vaccination rate at three-year health screenings was 78.4% in 1995, 85.6% in 1996, 86.4% in 1997, 89.2% in 1998, 93.0% in 1999, 92.1% in 2000, and 94.0% in 2001. Our survey of kindergarten children in May 2007 revealed a vaccination rate of 99.4%.

As shown in Figure 1, the revised number of patients with measles in Group A was 942. In Group B, it was 131, corresponding to 13.9% of the value in Group A. In Groups C and D, these values were 18% and 11%, respectively. In Group A, children aged 0-4 years accounted for 88.1% of cases. In Groups B and C, values were significantly lower (64.8% and 50%, respectively, $p<0.0001$). It was striking that 40% of measles patients in Group C were over 10 years old, compared to only 0.07% of measles patients in Group A ($p<0.0001$). The number of patients with measles before introduction of the measles vaccine (1964 to 1968) was 558: 504 children aged from 0-4 years (90.3%), 54 children aged 5-9 years (9.7%) and no patients over 10 years old. The age distribution of measles patients from1964 to 1968 was comparable to that of Group A.

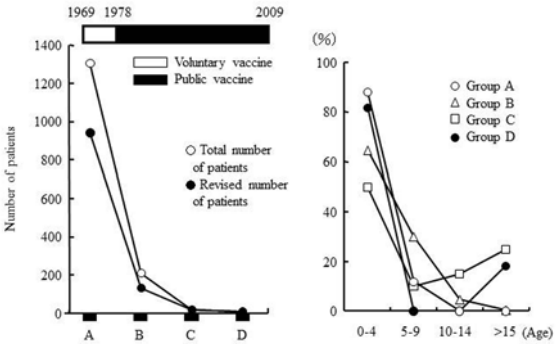

Fig. 1. The number of patients with measles at our clinic and serial changes in age. Group A, 1970-1974; Group B, 1982-1986; Group C, 1996-2000, and Group D, 2001-2005.

2) *Varicella*

Voluntary inoculation of attenuated varicella vaccine has been performed since 1987. The vaccination rate in Toda city was 29.1% in 1998, 32.3% in 1999, 31.5% in 2000, and 30.8% in 2001. In our survey of kindergarten children, the varicella vaccination rate was 16.8% in 2007. Interestingly, there were no marked differences in the revised number of patients with varicella among the four groups (Fig. 2A). With respect to age at onset, patients aged 0-4 years accounted for 55.6%, 71.4%, 85.7%, and 83.9% in Groups A, B, C, and D, respectively, indicating that the onset of varicella is at a relatively younger age (Fig. 2A). In a survey of 525 kindergarten children, 314 (72.0%) of 436 children who had not undergone vaccination developed varicella. Of the 88 children who had received vaccination, 18 (20.5%) developed varicella. There was a significant difference in occurrence between inoculated and non-inoculated children ($p<0.0001$).

3) *Mumps*

Voluntary inoculation with live, attenuated mumps vaccine alone was introduced in 1981. It was switched to inoculation with MMR at public expense for children aged 12-36 months in 1989, but this was discontinued in 1993 due to the development of post-vaccination aseptic meningitis. Voluntary inoculation with mumps vaccine alone was restarted in 1994. In Toda city, the vaccination rate for mumps was 31.0% in 1998, 26.5% in 1999, 28.9% in 2000, and 31.5% in 2001. In our survey of kindergarten children in 2007, the vaccination rate was 15.8%.

There were no remarkable differences in the revised number of patients with mumps among Groups A, B, C, and D (Fig. 2B), nor were there differences in age distribution among the Groups (Fig. 2B). In our kindergarten children survey, 106 (24.1%) of 440 children who had not undergone vaccination developed mumps. Of the 82 children who had received a vaccination, only 4 (4.9%) developed mumps.

We also examined the relationship between the presence and absence of preventive vaccination and clinical findings in 701 patients aged 0-15 years with mumps who consulted our clinic between 1989 and 2006. In 380 (61.0%) of 623 non-vaccinated patients, swelling of the bilateral parotid glands or both the parotid and submandibular glands was observed. In contrast, such clinical findings were noted in only 10 (14.7%) of 68 vaccinated patients. Peak body temperature was lower than 38°C in 243 (39.0%) of the former group and 49 (72.1%) of the latter group.

4) *Herpangina and Exanthema Subitum*

We analyzed the incidence of herpangina and exanthema subitum, which are not included in inoculation programs. As shown in Figure 3A, there were no marked differences in the revised number of patients with herpangina among Groups A, B, C, and D. Children aged 0-4 years accounted for approximately 80-92% of cases in all groups. Similarly, there were no marked differences in the revised number of patients with exanthema subitum among the four groups (Fig. 3B). Children aged ≤1 year accounted for approximately 98-100% of cases. These findings show there is no difference in the frequency of these two viral infections,

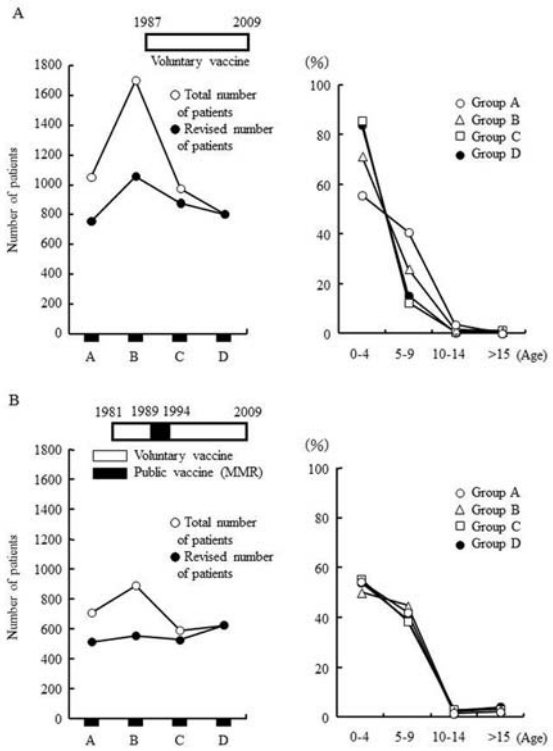

Fig. 2. The number of patients with varicella or mumps at our clinic and serial changes in age. The periods represented by Groups A-D are described in Figure 1. A: Varicella. B: Mumps.

which have had no preventive inoculation for over 45 years in this area.

Lastly, data in all the above figures were given in one table (Table I), which includes the voluntary or public inoculation period, groups, total and revised number of patients, and percentages of patient number in each age group.

Discussion

Preventive vaccination in Japan has contributed to decreases in the incidences of various infectious diseases since 1969. We herein evaluated the effectiveness of vaccination on large- scale public protection for measles, varicella and mumps at our pediatric clinic over a period of 45 years. Along with the absence of serial changes in the number of patients with herpangina or exanthema subitum, there were no marked differences in the number of patients with varicella or mumps at our clinic during the examination period. In contrast, the measles vaccine provided at public expense significantly reduced the incidence of measles cases.

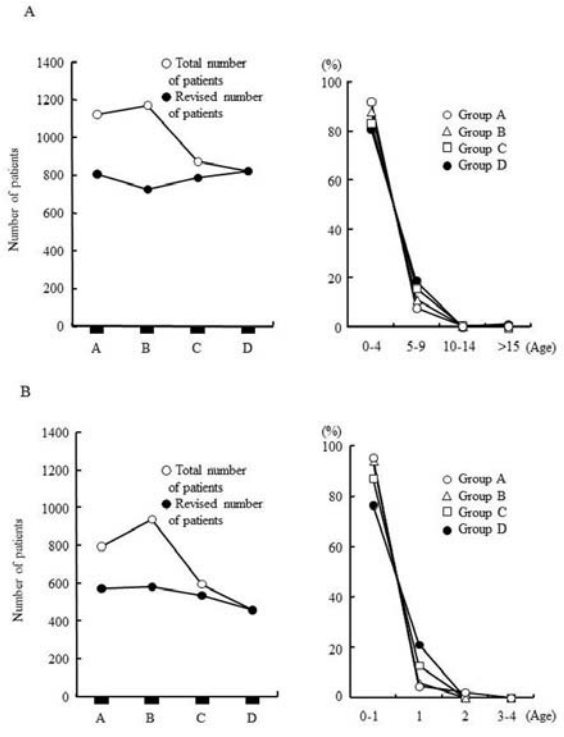

Fig. 3. The number of patients with herpangina or exanthema subitum at our clinic and serial changes in age. The periods represented by Groups A-D are described in Figure 1. A: Herpangina. B: Exanthema subitum.

Similar to a previous report[5], a marked decrease in measles patients was obtained in our area through publicly sponsored inoculation. However, as demonstrated in Figure 2, the increase in measles patients older than 15 years is alarming. Since outcome patient number has been changed every year, we calculated the modified number of patients by multiplying the total number of patients with each type of viral infection over five years by a modification coefficient (closed circle in Figures). Krugman et al.[5] previously indicated that the enhanced immunity acquired with the measles vaccine gradually attenuated when additional stimuli via spontaneous infection disappeared. Several reasons may be involved in the onset of measles at an advanced age[7]. First, approximately 5-10% of cases were non-vaccinated individuals who had not previously developed measles. Second, approximately 3% of cases may not have acquired antibodies after immunization. Third, a reduction in the antibody titer in vaccinated individuals may have occurred. In Japan, single-dose inoculation with a live vaccine had been promoted until March 2006 based on guidelines from the Ministry of Health, Labor and Welfare. In April 2006, the Preventive Vaccination Law was revised to double-dose inoculation with a measles-rubella vaccine at 12-23 months of age and within one year of entering elementary school. The occurrence of measles at an older stage is expected to decrease and requires further study. Since infectious surveillance of measles was started in Japan in 1983, the incidence rate before public vaccination has been unclear. The infectious disease surveillance center in Japan reported that the total number of each infectious disease in 3,000 fixed point hospitals every year in the last 10 years was as follows: 516 to 33,800 in measles, 202,000 to 275,000 in varicella, 65,000 to 254,000 in mumps, 75,000 to 154,000 in herpangina, and 94,000 to 125,000 in exanthema subitum.

The live, attenuated varicella vaccine developed in Japan in 1985[8] was recognized by the World Health Organization (WHO) for its effectiveness and safety. However, the vaccination rates remain low because of its high cost, risk of postvaccinal varicella infection, and the introduction of acyclovir. Given that there was no significant difference in the revised number of patients with varicella among the groups, it can be said that the status of mass public

Table1. Number of patients with viral ihfections in our clinic and serial changes in age

Name of illness	Vaccine	Group	Number of patients		Age groups (%)			
			Total	Revised	0~4	5~9	10~14	>15
Measles	Voluntary (1969~1977) Public (1978~2009)	A	1308	942	88,1	11,9	0,07	0,0
		B	211	131	64,8	30,0	4,8	0,5
		C	20	18	50,0	10,0	15,0	25,0
		D	11	11	81,8	0,0	0,0	18,2
Varicella	Voluntary (1987~2009)	A	1051	757	55,6	40,7	3,6	0,1
		B	1701	1055	71,4	26,1	1,6	0,9
		C	974	877	85,7	12,3	0,7	1,2
		D	802	802	83,9	15,2	0,5	0,4
Mumps	Voluntary (1981~1988, 1994~2009) Public(MMR)	A	711	512	54,3	42,1	1,5	2,1
		B	887	550	50,1	44,8	2,3	3,0
		C	587	528	55,7	38,3	3,1	2,9
		D	623	623	54,1	39,3	2,6	4,0
Herpangina	None	A	1121	807	92,0	7,6	0,3	0,2
		B	1172	727	88,2	11,2	0,6	0,0
		C	874	787	83,3	15,9	0,5	0,3
		D	822	822	80,0	18,9	0,7	0,9
			Number of patients		Age groups (%)			
		Group	Total	Revised	0~1	1	2	3~4
Exanthema subitum	None	A	794	572	95,5	4,5	0,0	0,0
		B	939	582	94,2	5,8	0,0	0,0
		C	593	534	87,2	12,8	0,0	0,0
		D	457	457	76,6	26,2	2,2	0,0

Measles: Group A, 1970 to 1974; Group B, 1982 to 1986; Group C, 1996 to 2000; Group D, 2001 to 2005.
Varicella and mumps: Group A, 1970 to 1974; Group B, 1982 to 1986; Group C, 1996 to 2000; Group D, 2001 to 2005.
Herpangina and exanthema subitum: Group A, 1970 to 1974; Group B, 1982 to 1986; Group C, 1996 to 2000; Group D, 2001 to 2005.

protection has not been achieved. Inoculation with live, attenuated double-dose varicella vaccine is recommended for all children in the United States and parts of Canada. In South Korea, varicella vaccination of children 12-15 months of age is performed as part of a national immunization recommendation[4]. In Japan, periodic inoculation with a varicella vaccine at public expense is now being reviewed[9] and may yield a decrease in disease incidence.

In Europe and the United States, double-dose inoculation with MMR is performed to prevent measles, mumps, and rubella[2,3]. In Japan, MMR vaccine at public expense was introduced in 1989, but was discontinued in 1993 due to post-vaccination aseptic meningitis at an incidence of 1 per 2,000 people[10]. Thereafter, public programs for inoculation with measles or rubella vaccines alone were started, and voluntary inoculation with mumps vaccine was employed again. From our data, the rate of mumps vaccination remains very low, but inoculation in some children markedly decreased symptoms. In another study, the incidence of aseptic meningitis related to mumps vaccination was approximately 0.01%, whereas the incidence of meningitis/encephalitis was approximately 1% in mumps patients who did not receive the vaccine[11]. Clinical findings were also milder in patients who developed mumps after vaccination[12]. Therefore, mumps inoculation should be performed in a larger number of individuals; in our survey, the vaccination rate was lower than 20% for each of varicella and mumps in 2007, compared to higher than 95% for measles. Similar results were reported in Toda city.

Finally, as evidenced by the problem of post-vaccination aseptic meningitis and a recent issue regarding *Haemophilus influenzae* type b (Hib) and heptavalent pneumococcal conjugate vaccines, it should be considered essential that countries adopt vaccines that have no side effects and are almost perfectly safe. Currently, the measles vaccine is administered with WHO assistance in developing countries[3], although the rubella

vaccine is not[10]. Our results may provide useful information for designing inoculation strategies with such vaccines for overall public protection.

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