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Efficacy of inactivated trivalent influenza vaccine in alleviating the febrile illness of culture-confirmed influenza in children in the 2000–2001 influenza season

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Abstract

During the 2000/2001 influenza season in Japan, children ranging in age from 6 months to 13 years with fever exceeding 37.5 °C were recruited. Vaccine efficacy was evaluated by comparing the rates of pre-seasonal vaccination between groups stratified by fever severity. Seven hundred and sixty one patients (33.1%), culture positive for influenza were enrolled for analysis. The numbers of patients for A/H1N1 and A/H3N2 were insufficient for statistical analysis. For influenza B the odds ratio for vaccinated children to have a maximum fever exceeding 39.5 °C was 0.52 (95% CI, 0.30–0.92) Our findings suggest modest impact of influenza vaccination on limiting severity of disease symptoms.

Keywords: Inactivated influenza vaccine; Efficacy on febrile illness; Culture-confirmed influenza

1. Introduction

Influenza causes yearly epidemics and is a major cause of lower respiratory tract illness in young children. Annual influenza attack rates vary from 10 to 30% in adults and 20 to 50% in children [1,2]. Earlier studies suggest the risk of serious complications and hospitalizations due to influenza infection are high in young children [3–5].

The FDA approved a live attenuated intranasal vaccine in 2003. Because its safety has not been established in high-risk individuals, it is not available for children under 5 years of age [6]. They can only be given inactivated vaccine at present.

Inactivated influenza vaccine protects against the illness and reduces its severity in adults and older children [7–10], but evidence of its efficacy in early childhood is limited, especially in respect to alleviation of symptoms.

In Japan many cases of influenza-related encephalopathy have been reported recently [11]. Vaccination is expected to

Abbreviations: CI, confidence interval; OR, odds ratio; MDCK, Madin–Darby canine kidney; PBS, phosphate-buffered saline; CPE, cytopathic effects; PAP, peroxidase–antiperoxidase; CMH, Cockran–Mantel–Henszel; *F*, Fisher' exact test; ACIP, Advisory Committee on Immunization Practices; SAGPJ, Society of Ambulatory and General Pediatrics of Japan

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reduce the incidence and severity of complications, including influenza-related encephalopathy.

Inactivated influenza vaccine does not give an ideal immunization to prevent infection completely. It would be better to estimate the efficacies of vaccination on prevention and on alleviation of severity of illness separately. In this study we tried to estimate the efficacy of inactivated influenza vaccine in alleviating the febrile response in culture-confirmed influenza in children.

2. Materials and methods

2.1. Study design

This study was conducted as a case-control, multicentered study of twenty-one pediatric clinics during the 2000/2001 influenza season in Japan.

Febrile children were recruited consecutively until the planned number assigned to each institution was reached. Cases with culture-confirmed influenza were enrolled for analysis. Subjects were stratified to two or three groups based on the severity of fever. The proportion of pre-seasonal vaccination in each stratum was compared statistically.

The purpose of the study was explained to parents or guardians of all patients and signed consent was obtained.

2.2. Subjects

During 1 December 2000 to 30 April 2001 each collaborator started when the beginning of the outbreak was recognized and stopped when the allocated number was reached. Children ranging in age from 6 months to 13 years who had a febrile illness of over 37.5 °C that lasted for fewer than 3 days were recruited. To avoid potential selection bias, recruitment was performed consecutively and regardless of influenza-like symptoms. Patients given two doses of pre-seasonal vaccine with an adequate interval and those given no pre-seasonal vaccine were enrolled as vaccinated cases and as unvaccinated cases, respectively. The following were excluded: patients given only one dose of vaccine; those given two doses with less than two weeks between doses; those with illness onset within two weeks after the second vaccine; those having a history of underlying chronic illness; and those having an apparently different febrile illness.

2.3. Virus isolation

Nasal or throat swabs, or nasal aspirates were collected from all patients within 72 h after the onset and they were stored at −20 °C and subsequently transported to the laboratory for virus isolation.

Samples were centrifuged at 3000 rpm for 30 min at 4 °C and the supernatants were inoculated onto Madin–Darby (MDCK) cells in 24-well microplates. After removal of the specimens and washing with phosphate-buffered saline (PBS), the cells were covered with Eagle' minimal essential medium containing 2 μg/ml acetylated trypsin and 2.5 μg/ml amphotericin B. Cultures were incubated for 7 days at 35 °C and were observed for the development of cytopathic effects (CPE). The fluids of cultures with complete CPE were harvested and stored at −20 °C for the identification of isolated strains.

For subtype differentiation, the peroxidase–antiperoxidase (PAP) staining method was performed [12]. MDCK cells in 96-well microplates were inoculated with the isolated strains in triplet and plates were incubated for 20 h at 35 °C. The cells were fixed with absolute ethanol and then treated with two subtype-specific (H1N1 and H3N2) and B type-specific monoclonal antibodies, and rabbit anti-mouse immunoglobulin. The cells were treated successively with goat anti-rabbit immunoglobulin G antibody and PAP (rabbit antiperoxidase) complex. Finally, a peroxidase reaction with 0.01% H_2O_2 and 0.3 mg/ml 3,3′-diaminobenzidine tetrahydrochloride in PBS was allowed to develop for 5 min. The cells were then rinsed with tap water and dried. The stained cells were observed under an ordinary light microscope.

Patients with influenza infection confirmed by virus isolation were enrolled as subjects for analysis.

2.4. Vaccination

The vaccine was inactivated trivalent HA split vaccine including Influenza A/NewCaledonia/20/99, A/Panama/2007/99 and B/Yamanashi/166/98, those were strains recommended by WHO and adopted by the Japanese government. Two doses of vaccine were administered more than two weeks apart. Different doses of vaccine were given according to Japanese standards; 0.1 ml for children 6–11 months of age, 0.2 ml for 1–5 years of age and 0.3 ml for 6–13 years of age.

2.5. Record of symptoms

Each parent or guardian of all patients was asked to record body temperature and other symptoms daily during the illness on formatted sheet.

2.6. Statistical analysis

Subjects were stratified to two or three strata by severity of febrile illness defined by degree of maximum body temperature during the illness or by the number of days with fever in each case. The vaccine effects were evaluated by comparing the rates of vaccinated children for each stratum of fever level.

First, we stratified subjects into two groups by the level of maximum body temperature during the illness in each case. Four trials of analyses for this purpose were performed using different cutoff points of body temperature including three points dividing the patients into equal quartiles (25% tile: 39.1 °C, 50% tile: 39.3 °C, 75% tile; 39.8 °C) and 39.5 °C as the dip point in a histogram of maximum body temperature.

Second, we stratified the patients into two or three groups by the number of days having a fever higher than several certain points.

The rates of pre-seasonal vaccination were compared between groups of different febrile severity.

The difference in proportions was evaluated using Fisher's exact test. Two-sided 95% confidence intervals were calculated on the odds ratios. Cochran–Mantel–Haenszel test was used to estimate the adjusted odds ratio. Proportional odds regression model was used for ordered categorical outcome such as severity of fever. All analyses were performed with SAS software, version 8.2 (SAS Institute Cary, NC).

3. Results

Twenty-one pediatricians in private clinics and hospitals in Japan participated in this study. All of 2814 children who met the inclusion criteria were registered and 2300 of them were enrolled. Others were excluded mainly because of incomplete information. Specimens for virus culture were collected from all patients and 761 cases (33.1%) proved to be culture positive for influenza and were included in the analysis. A/H1N1 was isolated in 167, A/H3N2 in 93 and B in 501 (Table 1).

The distribution of the patients' age was analyzed in the patients positive for virus isolation, A/H1N1, A/H3N2, B and negatives. In patients infected with influenza B, the proportion of older patients seemed to be greater, compared with the other groups.

In patients who were culture negative for influenza, there was no significant difference in the distribution of maximum body temperature during illness between the vaccinated and unvaccinated groups, which suggested that there was no major problem in sampling and sensitivity of virus culture.

There were insufficient cases of A/H1N2 and A/H3N2 for statistical analysis, so vaccine efficacy was analyzed only for influenza B.

We analyzed the distribution of patient's age with influenza B infection and compared the vaccinated and unvaccinated groups and the results are shown in Table 2. A difference in age distribution between the two groups was detected. Because the unvaccinated patients were somewhat older, adjustments for age were necessary for further analysis.

We set four different temperature points to divide the patients into two groups of higher and lower fever. At first the point was set at 39.5 °C representing the dip between two peaks in the histogram of maximum temperature and the other three points were set at temperatures dividing the patients into quartiles.

Table 1
The results of virus isolation and immunization status

Influenza type	Influenza vaccine		Total
	(+)	(−)	
A/H1N1	20	147	167
A/H3N2	12	81	93
B	78	423	501
Total	110	651	761

Table 2
Age distribution of influenza B

Age (years)	Influenza vaccine	
	(+) (%)	(−) (%)
0.5–3.0	20 (25.6)	75 (17.7)
3.1–6.0	36 (46.2)	156 (36.9)
6.1–12.9	22 (28.2)	192 (45.4)
Total	78	423

Table 3
The rates of vaccinated children in different fever groups; 37.5–39.5 °C and ≥39.6 °C of maximum body temperature in influenza B (cutoff point = 39.5 °C)

Vaccination	Maximum body temperature	
	37.5–39.5 °C (%)	≥39.6 °C (%)
Vaccine (+)	58 (18.1)	20 (11.4)
Vaccine (−)	262 (81.9)	156 (88.6)
Total	320	176

Table 4
Efficacies on the risk of high fever in vaccinated patients compared with unvaccinated patients (39.5 °C: dip of histogram)

	Odds ratio	95% CI	*P*-value
Crude	0.58	0.34–1.01	0.054 (*F*)
Adjusted on age	0.52	0.30–0.92	0.024 (CMH)

CI: confidence interval; *F*: Fisher's exact test; CMH: Cochran–Mantel–Henszel test.

The rate of pre-seasonal influenza vaccination was 11.4% (20/176) in the higher fever group, maximum body temperature over 39.5 °C and 18.1% (58/320) in the lower fever group, maximum body temperature below 39.5 °C (Table 3).

The odds ratio for vaccinated children to have a maximum fever over 39.5 °C was calculated to be 0.58 (95% CI, 0.34–1.01), indicating no significant difference. After adjustment for age, it fell to 0.52 (95% CI, 0.30–0.92) with the Cochran–Mantel–Henszel test ($P = 0.024$), indicating a significant difference (Table 4).

When the cutoff point was set at 39.3 °C, a significant but smaller difference was detected (Table 5).

No significant difference was detected in analysis with the other two points.

In a proportional odds model analysis, the odds ratio for having a temperature exceeding 39.5 °C fell to 0.588 (95%

Table 5
Efficacies on the risk of high fever in vaccinated patients compared with unvaccinated patients (39.3 °C: median)

	Odds ratio	95% CI	*P*-value
Crude	0.7	0.43–1.14	0.173 (*F*)
Adjusted on age	0.58	0.35–0.96	0.033 (CMH)

CI: confidence interval; *F*: Fisher's exact test; CMH: Cochran–Mantel–Henszel test.

CI, 0.38–0.91) by the vaccination, and also fell to 0.887 (95% CI, 0.84–0.94) by aging a year. The effect of the vaccination was statistically independent from that of aging.

We also analyzed the efficacy of vaccination on shortening the duration of fever due to influenza infection. We set different criteria from 37.5 to 40.0 °C by 0.5 °C intervals for counting the days of fever duration, defined as days of actual fever, which were not necessarily consecutive, because fever does not always develop every day of the illness.

In each fever-criteria we tried to compare the rates of vaccination between two or three groups stratified by the fever duration in days. No significant difference was observed in an analysis for vaccine efficacy to shorten the febrile duration.

4. Discussion

Influenza is common in childhood with the highest morbidity occurring in preschool children and an excess of school absence and hospitalization has been reported [1–5]. Although it is clinically difficult to distinguish influenza from other respiratory illnesses, which often circulate concurrently [13–17], limited data are available on laboratory-confirmed influenza in children [1,4,5,18,19].

Recently, reports of influenza-associated severe illnesses and deaths in otherwise healthy children have been increasing and emphasize the importance of protecting children from influenza [11,20–23].

Izurieta et al. reported that the rate of hospitalization for influenza among children younger than 2 years of age was approximately 12 times higher than for otherwise healthy children aged 5–17 years and approached the rate among children with chronic health conditions in the 5–17 years age group. They urged that routine influenza vaccination should be considered in these children [24].

Quach et al. reported on 182 hospitalized children with laboratory-proved influenza who received admission diagnoses of suspected sepsis (31%); lower respiratory infections (27%); and asthma or bronchiolitis (15%). Of these patients 34% were <6 months. Seventy percent of those hospitalized did not have any underlying medical disorders. They argued that extending vaccination to all young children, in addition to high-risk groups and pregnant women has the potential to reduce the impact of influenza on children [25].

Because young, otherwise healthy children are at increased risk for influenza-related hospitalisation. In 2002 the Advisory Committee on Immunization Practices (ACIP) began encouraging annual influenza vaccination of children 6–23 months of age, when feasible [26]. At its 2003 meeting, ACIP voted to recommend that children 6–23 months of age be vaccinated annually against influenza. This recommendation expands the age group for which vaccination is recommended [27].

Difficulty in the clinical diagnosis of influenza infection is re-emphasized because of its wide spectrum of manifestations in childhood and the potential confusion with other viral illnesses. The efficacy of influenza vaccine against infection and illness in childhood may be underestimated by including other respiratory virus infections circulating concurrently or may be overestimated by missing mild influenza infections [13–18]. Studies of the efficacy of influenza vaccine where the diagnosis was not confirmed virologically should be evaluated with great caution, especially in childhood.

Since inactivated influenza vaccine cannot completely prevent recipients from infection and illness, it is preferable to estimate effectiveness on prevention and that on alleviation of symptoms separately. In this study we focused on vaccine efficacy on alleviation. In previous studies, efficacy on alleviation in otherwise healthy children was estimated by complications that were indirect indices of severity [28–30]. As an objective index of severity we used fever, an established major component of influenza illness in children.

In this study all patients having a febrile illness of over 37.5 °C were recruited consecutively to avoid selection bias and all provided samples for virus isolation to exclude other viral infection and to avoid missing mild influenza infections. Only children with culture-confirmed influenza were included in the analysis. Statistical analysis was performed for influenza B only. In comparisons between groups stratified by maximum fever, odds ratios of vaccinated children for developing a fever exceeding 39.5 °C (dip of histogram) and 39.3 °C (median) were 0.52 and 0.58, respectively, after adjusting for age, indicating significant differences. Analysis by the other two points resulting from dividing into quartiles did not result in a statistical difference.

The vaccine strain and the circulating strain of influenza B were not well matched for this season. The 2000/2001 Japanese epidemic strains of influenza B were B/Sichuan and/Johannesburg and the vaccine strain influenza B was B/Yamanashi. Our results show that inactivated trivalent influenza vaccine was modestly effective in reducing the risk of developing a higher febrile illness from influenza B in a season when circulating strains did not match well with the vaccine strain. Despite a small beneficial effect in the year studied, influenza vaccination with better matching would be more effective.

There are statistical limitations to the study. Subjects who were recruited from outpatients might not represent strictly the target population. Statistical examinations for confounding factors were insufficient. In Japan the usual doses of influenza vaccine are the following: 0.1 ml for <12 months of age, 0.2 ml for 1–5 years of age, 0.3 ml for 6–12 years of age and 0.5 ml for >13 years of age. We have no data to refute the possibility that the results of this study were influenced by immunization dosage. The efficacy of inactivated influenza vaccine might be limited and insufficient for priming of influenza infection for infants.

Recently, trivalent cold adapted live attenuated intranasal influenza vaccine was approved in the USA. The overall efficacy of this vaccine in children was 93% for those presenting with culture-confirmed influenza [31], but it cannot be given to children under 5 years of age. An inactivated triva-

lent vaccine has been beneficial and necessary up to now. The necessity for universal immunization for children 6–24 months of age and for the identification and recall of children with chronic medical conditions for influenza vaccination has recently been stressed [32].

Further investigations are required to promote better understanding of the efficacy of vaccine against the illness of influenza A/H1N2 and A/H3N2, as well as B when strains of vaccine and circulating virus are better matched. But the general use of a rapid diagnostic test for the diagnosis, and of antiviral medication, will make it difficult to carry out future studies to estimate the efficacy of vaccine to alleviate illness.

5. Conclusions

In the 2000–2001 influenza outbreak in Japan, inactivated trivalent influenza vaccine was modestly effective in reducing the risk of developing a higher febrile illness from influenza B in children in a season when the vaccine strains were not well matched with circulating strains.

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This study was approved and monitored by the Society of Ambulatory and General Pediatrics of Japan ethical committee.

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A comparative study of the incidence of aseptic meningitis in symptomatic natural mumps patients and monovalent mumps vaccine recipients in Japan

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Abstract

To compare the incidence of aseptic meningitis associated with symptomatic natural mumps infection and in mumps vaccine recipients, we conducted a prospective comparative study. Consecutive samples of 1051 children with mumps were enrolled by 10 pediatricians and 21,465 vaccine recipients by 143 pediatric primary care practitioners, from January 1, 2000 to January 1, 2003. Parents used a daily diary to record symptoms during the period of illness (15 days) or 30-day period following immunization. Mumps infection was confirmed by virus isolation and/or detection of mumps virus genome in salivary and CSF samples. The incidence of aseptic meningitis was 13/1051 (1.24%) in patients with symptomatic natural mumps infection and was estimated to be 0.7–1.1% of overall infection in considering asymptomatic infection, and 10/21,465 (0.05%) in vaccine recipients. Although aseptic meningitis is a clear side effect of the mumps vaccine, the incidence is considerably lower than among those with symptomatic natural infection. Our results provide an informative data for consideration to resume mumps vaccine as a part of routine immunization schedule for Japanese children.

Keywords: Aseptic meningitis; Mumps vaccine; Natural mumps

1. Introduction

Epidemic parotitis is a common infantile infectious disease caused by the mumps virus belonging to the paramyxoviridae RNA virus; mumps virus is also a well known cause of aseptic meningitis in children [1,2]. Live attenuated Measles-Mumps-Rubella (MMR) vaccine is approved in most countries, with effective immunization reducing annual outbreaks of mumps, and vaccine-associated aseptic meningitis is not a matter of concern [3,4]. In Japan, MMR vaccine was licensed in December 1988 and recommended for infants as a part of their basic immunization. Because of unexpectedly high incidence of aseptic meningitis caused by the mumps vaccine component, MMR vaccine was discontinued in 1993 [5,6]. Since then, monovalent measles and rubella vaccines have been recommended for children over 1 year of age, but mumps monovalent vaccine has been optional. Consequently, we have experienced annual outbreaks of mumps

Abbreviations: MMR, Measles-Mumps-Rubella; RT-PCR, reverse transcription-polymerase chain reaction; CSF, cerebrospinal fluid; SAGPJ, Society of Ambulatory and General Pediatrics of Japan; CPE, cytopathic effect; P, phosphoprotein; HN, hemagglutinin-neuraminidase protein; CI, confidence interval

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estimated more than one million cases every year, because of the low acceptance of the monovalent mumps vaccine less than 30% [7].

The purpose of this study was to estimate the incidence of aseptic meningitis among non-immunized children with natural mumps infection in Japan, to estimate the incidence of aseptic meningitis among monovalent mumps vaccine recipients age 1 through 18 years, and to compare the incidence of aseptic meningitis and other associated side effects such as fever among the three mumps vaccine strains (produced by three different manufacturers). The incidence of aseptic meningitis among vaccine recipients was compared to that among those with natural infection.

2. Methods

2.1. Study design

We conducted parallel prospective studies to estimate and compare the incidence of aseptic meningitis among children immunized against mumps and non-immunized children who contracted mumps. The first study of symptomatic natural mumps infection among non-immunized children resulted from collaboration among the 10 pediatricians who are the principal members of the Vaccine Study Group of the Society of Ambulatory and General Pediatrics in Japan (SAGPJ) and general pediatricians without any geographic distribution of Japan. The second study on aseptic meningitis among mumps vaccine recipients was a collaborative effort by 143 private office and general hospital-based pediatric primary care practitioners. Practitioners were recruited from the membership of the SAGPJ and represent 15% of the total membership, and those were very active candidates and interested in this study.

In the first study, all children under 18 years of age were eligible for enrollment if they were seen at the clinical facilities of the 10 investigator-practitioners with signs and symptoms of natural mumps. All patients suspected clinically with mumps were registered initially but only those whose salivary swabs tested positive for mumps at a central facility (described below) were ultimately enrolled. Parents or guardians were asked to monitor signs and symptoms of illness, including body temperature, vomiting, headache, seizures and salivary gland swelling, and complete a standardized daily diary for the 15-day period after the first day of symptoms reported by parents. Written data, including demographic characteristics of each patient, was collected by individual practitioners or staff members of each facility and mailed to the central research facility at the Department of Pediatrics and Child Health of Kurume University Medical Center for data analysis. Salivary samples and cerebrospinal fluid (CSF) were obtained and further processed for the patients who developed the clinical illness.

In the second study, all children under 18 years of age were eligible to be enrolled by the practitioners if they had received the mumps vaccine during the study period, from January 1, 2000 to January 1, 2003. Three Japanese licensed mumps vaccine strains were used: Torii (Takeda Pharmaceutical Company Limited), Miyahara (Kaketsuken, the Chemo-Sero-Therapeutic Research Institute), and Hoshino (Kitasato Institute, Research Center for Biologicals). Nearly all eligible individuals were enrolled and verbal informed consent was obtained at the visit for the immunization. Parents or guardians completed a diary as described above, using the same protocol as the first study, for the 30-day period after immunization. Data collection including the processing of samples also used the same protocol.

Aseptic meningitis was defined as CSF pleocytosis of greater than 15 white blood cells observed per high power field. Lumbar puncture to obtain CSF was performed only among those patients whose symptoms were judged as severe enough to warrant hospitalization by their physicians.

This study was approved by the Ethics Committee of SAGPJ, and this Committee meets the general requirement for the personnel organization including outside lawyer.

2.2. Virological examinations

Swabs from Stensen's duct orifice and CSF were frozen and transferred in package with dry ice to the clinical laboratory in the Kitasato Institutes within 48 h after sampling. Mumps virus infection was confirmed by positive virus isolation in Vero cells and/or by the detection of mumps virus genome through nested RT-PCR. They are described in full elsewhere [8,9]. Briefly, 0.1 ml of sample was inoculated on a monolayer of Vero cells. Samples showing a viral-specific cytopathic effect (CPE) were confirmed by neutralization test using antiserum to mumps virus, while those not showing CPE after three passages were considered to be negative for virus isolation. Nested RT-PCR was done in the phosphoprotein (P) and/or hemagglutinin-neuraminidase protein (HN) regions, as previously described [10–14]. Briefly, total RNA was extracted from 200 μl of the clinical samples. Mumps genomic RNA was reverse-transcribed with AMV reverse transcriptase (Life Sciences Inc. St Petersburg, Florida) at 50 °C for 1 h. Five microliters of viral cDNA was amplified by PCR in a total volume of 50 μl mixture as recommended by the manufacturers, using 1.25 units of Taq DNA polymerase (TaKaRa BIOMEDICALS, Tokyo). Genomic differentiation of the vaccine strain from wild strains was performed by sequence analysis of the P and HN genes in all hospitalized meningitis cases [9–11,15,16]. We purified the PCR products and analyzed the DNA sequence bidirectionally with a Dye Terminator Sequencing Kit (Applied Biosystems Japan Inc., Tokyo, Japan) using an automated nucleotide analyzer (377A DNA Sequencer, Applied Biosystems, Foster City, CA, USA).

2.3. Statistical analysis

Statistical analyses were conducted using SAS version 8.2 (SAS Institute, Inc., Cary, North Carolina, USA). To compare

data from the Mumps Vaccine Study with those from the Natural Mumps Meningitis Study (e.g., symptoms at time of hospital admission), we used the Welch *t*-test, Fisher's exact test or student *t*-test. Relative risk was calculated to compare the incidence of aseptic meningitis after immunization with the three vaccine products.

3. Results

3.1. Aseptic meningitis in symptomatic natural mumps

In the study of symptomatic natural mumps infection, we examined 1353 samples obtained from patients who were suspected as mumps infection from clinical symptoms or household contacts and identified 1085 as mumps virus infection. Eight hundred and seventy two samples were positive for both virus isolation and RT-PCR and 213 samples were positive for RT-PCR alone. The remaining 268 samples were negative for both tests. Although 1085 patients were confirmed as having natural mumps infection, the following 34 were excluded: 7 where age was greater than 18 years, 3 with incomplete information and 24 with asymptomatic infection. Therefore, 1051 patients were ultimately enrolled with symptomatic natural mumps infection. The ages of subjects ranged from 8 months to 18 years, the mean was 4.91 years and the median, 4.0 years. The male to female ratio was 1.07:1 (544 males and 507 females). Eight hundred and thirty-two patients (79.2%) had a febrile illness (≥37.5 °C) with a mean febrile period of 2.38 days and an average maximum temperature of 38.73 °C. Vomiting occurred in 180 patients (17.1%), with an average frequency of vomiting episodes of 2.01 times. Headache developed in 245 patients (23.3%) and seizures in 8 (0.8%). One patient (0.1%) developed deafness after recovery of the parotitis.

Thirteen patients were confirmed as having aseptic meningitis complicating their natural mumps infection. The results of their viral examinations are shown in Table 1. Their ages ranged from 1 to 10 years and 12 of the 13 were male. All patients were febrile (≥37.5 °C) and 12 (92.3%) were symptomatic with vomiting (the average number of vomiting episodes was 2.25 times), 11 (84.6%) experienced headache, and one had seizures (7.7%). In all 13 patients, mumps genomes detected in throat swabs were identified as wild type. CSF samples were examined in 10 of the 13 and wild type mumps virus was identified in 7 (6 cases confirmed by RT-PCR alone and one case by both virus isolation and RT-PCR). Three CSF samples were not transferred to the laboratory because of the problems in preservation of CSF samples. The incidence of serious aseptic meningitis with intractable vomiting and headache among patients contracting natural mumps was 13/1051 (1.24%), with virologically confirmed cases being 7/1051 (0.67%). In previous reports, approximately 15–40% of mumps infection is subclinical [1,2,4]. In considering the probability of asymptomatic infection, the incidence was estimated to be 0.7–1.1%.

3.2. Aseptic meningitis after mumps vaccination

In the study of mumps vaccine recipients, we tested 12 samples of CSF obtained from vaccine recipients who developed clinical aseptic meningitis. Two subjects were excluded: one with enterovirus infection, and another whose CSF did not have pleocytosis. The results of viral examinations in the 10 cases are shown in Table 2. The patients' age ranged from 1 to 16 years and nine of the 10 were male. Fever occurred in nine cases (90.0%), vomiting in eight (80.0%) with an average frequency of vomiting episodes of 3.38, headache in eight (80.0%), and seizure in none. Mumps virus genome was detected by nested RT-PCR and the vaccine strain genome was identified in eight (five were positive by virus isolation). No etiological agent was identified in the remaining two patients.

In this study, 21,465 vaccine recipients were enrolled; 7850 were immunized with the Torii strain, 6758 with the Miyahara strain and 6847 with the Hoshino strain, and we

Table 1
Aseptic meningitis in natural mumps patients

Case number	Age (years)	Sex	Swabs of Stensen's orifice			Cerebrospinal fluid (CSF)[a]		
			Virus isolation	RT-PCR	Strain (vaccine/wild)	Virus isolation	RT-PCR	Strain (vaccine/wild)
1	6	M	–	+	Wild	–	+	Wild
2	10	M	+	+	Wild	–	+	Wild
3	2	M	+	+	Wild	–	+	Wild
4	4	M	+	+	Wild	–	+	Wild
5	3	M	+	+	Wild	–	–	
6	4	M	+	+	Wild	+	+	Wild
7	4	M	+	+	Wild	–	–	
8	4	F	+	+	Wild	–	+	Wild
9	1	M	+	+	Wild	–	+	Wild
10	6	M	+	+	Wild	–	–	
11	4	M	+	+	Wild	NT[b]	NT	
12	6	M	+	+	Wild	NT	NT	
13	2	M	+	+	Wild	NT	NT	

[a] Three CSF samples were not transferred to the laboratory for virus isolation or RT-PCR.
[b] NT: not tested.

Table 2
Aseptic meningitis after vaccination with monovalent mumps vaccine

Case number	Age (years)	Sex	Vaccine strain	Virus isolation	RT-PCR	Strain (vaccine/wild)
1	6	M	Miyahara	–	–	
2	16	M	Torii	+	+	Vaccine
3	3	F	Torii	–	+	Vaccine
4	6	M	Torii	–	–	
5	10	M	Miyahara	–	+	Vaccine
6	3	M	Torii	+	+	Vaccine
7	3	M	Hoshino	+	+	Vaccine
8	1	M	Hoshino	–	+	Vaccine
9	2	M	Hoshino	+	+	Vaccine
10	4	M	Torii	+	+	Vaccine

The following two cases were excluded; one without pleocytosis and one with enterovirus infection diagnosed by the detection of enterovirus genome from the CSF.

identified 10 cases of vaccine-associated aseptic meningitis. The incidence of vaccine-associated aseptic meningitis was 10/21,465 (0.05%) and virologically confirmed meningitis 8/21,465 (0.04%). Of the vaccine recipients, ages ranged from 0 to 18 years, with a mean of 3.17 and median of 3.0 years and gender ratio of male to female was 11,719 to 9746. Fever higher than 37.5 °C developed in 5605 patients (26.1%), and among them 13.7% developed a febrile illness during 0–15 days and 12.3% during 16–30 days after vaccination. Febrile episodes were frequently observed without any differences for early and late course of the vaccination. For each vaccine strain, febrile episodes occurred in a similar pattern. In 18,168 recipients (84.6%), records of symptoms, including salivary gland enlargement, vomiting, headache and febrile seizure, were available. Salivary gland enlargement was observed in 551 cases (3.0%), vomiting in 2400 (13.2%) and headache in 852 (4.7%), and seizure was observed in 48 cases (0.3%) who were considered febrile seizure from clinical features having no neurological signs. For the different strains, salivary gland swelling, vomiting, headache and seizure were observed in 1.8, 13.0, 3.9 and 0.2% in Torii, 3.9, 14.6, 5.4 and 0.3% in Miyahara and 3.5, 12.0, 4.8 and 0.3% in Hoshino, respectively.

3.3. Comparison of the incidence of hospitalized subjects with aseptic meningitis

The comparison of the incidence of aseptic meningitis in both groups is summarized in Table 3. When we compared the incidence of aseptic meningitis according to vaccine manufacturer, five patients received the Torii (vaccine strain was detected from four), two received the Miyahara (vaccine strain was detected from one) and three received the Hoshino (vaccine strain was detected from all three). The incidence of aseptic meningitis associated with the vaccine strain of each manufacturer was 0.06% for Torii, 0.03% for Miyahara, and 0.04% for Hoshino, and the RT-PCR positive rate was 0.05% for Torii, 0.01% for Miyahara and 0.04% for Hoshino, respectively.

The incidence of aseptic meningitis was 1.24% among the non-immunized population confirmed by immunization records with mumps infection and, whereas, 0.05% in vaccine recipients which was 1/27 of the complication in natural infection. This ratio of the incidence of aseptic meningitis after Torii vaccine was 1/19, that after Miyahara was 1/42, and that after Hoshino was 1/28. The incidence of aseptic meningitis after immunization with different Japanese mumps vaccine strains and relative risks among strains showed no significant differences (statistical data not shown).

No other severe adverse reactions associated with vaccination or sequelae after the complications were observed during the study period.

4. Discussion

Three monovalent mumps vaccines have been used in Japan since 1993 [5,6], when the trivalent MMR vaccine

Table 3
Comparison of the incidence of aseptic meningitis among the patients with natural mumps infection and vaccine recipients of three different strains

	Natural mumps[a]	Mumps vaccine recipients				
		Torii[b]	Miyahara[b]	Hoshino[b]	Unknown	Total
Total number of subjects	1051	7850	6758	6847	10	21465
Number of meningitis cases (%)	13 (1.24)	5 (0.06)	2 (0.03)	3 (0.04)	0 (0.00)	10 (0.05)
Number of positive RT-PCR cases in CSF (%)	7 (0.67)	4 (0.05)	1 (0.01)	3 (0.04)	0 (0.00)	8 (0.04)
Ratio of meningitis cases in vaccine recipients vs. in natural mumps		1:19	1:42	1:28		1:27

[a] RT-PCR was carried out in only 10 cases of aseptic meningitis associated with natural mumps and 7 cases were positive. One case with deafness was reported additionally.

[b] The incidence of aseptic meningitis after immunization with different Japanese mumps vaccine strains and relative risks among strains showed no significant differences.

Table 4
Other clinical manifestations on the day of admission in aseptic meningitis patients associated with natural mumps and mumps vaccination

		Natural mumps ($n = 13$)	Vaccine recipients ($n = 10$)	Statistical analysis
Age (years)	Min.–max.	1–10	1–16	Welch t-test $P = 0.499$
	Mean ± S.D.	4.3 ± 2.3	5.4 ± 4.5	
Sex	Male/female	11/2 (84,6%)	9/1 (90.0%)	Fisher's exact test $P = 1.000$
Days after onset	Min.–max.	0–6	1–5	Student t-test $P = 0.651$
	Mean ± S.D	2.8 ± 2.2	2.4 ± 1.4	
Fever (≥37.5 °C)		13 (100.0%)	9 (90.0%)	Fisher's exact test $P = 0.435$
Headache		11 (84.6%)	8 (80.0%)	Fisher's exact test $P = 1.000$
Febrile seizure		1 (7.7%)	0 (0.0%)	Fisher's exact test $P = 1.000$
Vomiting		12 (92.3%)	8 (80.0%)	Fisher's exact test $P = 0.560$

was discontinued, but annual outbreaks of mumps continue [13,14]. In previous studies conducted by the Japanese Ministry of Health, Labor and Welfare, only the incidence of aseptic meningitis after the MMR vaccination has been reported [6,17], providing a narrow perspective of the issue to the public. We believe that the incidence of aseptic meningitis after vaccination should be compared with that observed after natural infection with considering asymptomatic infection, as reported in this paper. Most previous studies were based on clinically diagnosed cases [18], but we performed virus isolation and the detection of mumps virus genome to minimize the uncertainty of the clinical diagnosis. Aseptic meningitis developed in 1.24% of virologically confirmed mumps patients and in 0.05% of vaccinees. In 13 patients with aseptic meningitis during natural infection, 7 CSF samples were positive for RT-PCR in 10 samples, and all throat swabs were positive for virus isolation or RT-PCR. The risk of aseptic meningitis after vaccination was lower in comparison to those with symptomatic natural infection even when considering asymptomatic infection. There was no significant difference in the incidence of aseptic meningitis among three strains, although the statistical data was not shown because that was not a matter of concern.

Part of this study involved collaboration among 153 pediatricians, resulting in some limitations in case definition. Individual pediatricians may use different clinical criteria for obtaining CSF and advising hospitalization, thereby raising questions about the comparability of the criteria for hospitalization. The similarity of clinical symptoms of patients hospitalized with aseptic meningitis (Table 4) suggests that the criteria for hospitalization would be the same. Another potential bias might be the identification of severe cases of aseptic meningitis while overlooking mild ones. There may be numerous patients with mild meningitis with or without headache and vomiting. Patients with no symptoms other than parotitis and with only laboratory findings may also exist, but the mild cases would recover from the illness without treatment. The purpose of this study is to evaluate the incidence of serious aseptic meningitis to be hospitalized for the treatment as a complication of natural infection and as vaccine-associated clinical adverse effects. The practice areas of the pediatricians are not representative of the entire country, making generalizations for overall incidence difficult.

In Japan, hospitalization with vaccine related meningitis has been an important social and immunization strategic problem [6,17,19]. In our paper, we focused on vaccine effectiveness in preventing severe aseptic meningitis requiring hospital admission. According to our study, the risk of aseptic meningitis after vaccination was 1/27 of that associated with symptomatic infection, and in considering asymptomatic infection that was 1/23–1/16 of overall natural infection. The incidence of vaccination-associated aseptic meningitis was one case in 2000 vaccinees, however, which may still not be acceptable when compared with other live mumps vaccines. Aseptic meningitis after immunization with the Jeryl Lynn strain occurs in one in 100,000 vaccinees [1,20]. However, the Jeryl Lynn strain is not currently available in Japan. The Urabe strain was the most well-known mumps vaccine strain from Japan and formerly used worldwide [21–25]. The Japanese national MMR vaccine originally consisted of the Urabe strain and the Japanese government reported a risk of aseptic meningitis with the national MMR vaccine of one case in 500–1000 recipients [6,17]. Aseptic meningitis was also reported, but with a lower incidence, after vaccination with MMR vaccines produced by four independent manufacturers [17]. For a different batch of MMR vaccine, which included the Urabe strain and was produced by the same manufacturer, the incidence of aseptic meningitis was less than 1/10,000, suggesting different characteristics compared with the original strain included in the initial Japanese national MMR vaccine. This information was revealed a few years later. Currently, we are unable to use the Urabe strain of mumps as a monovalent vaccine for optional immunization because its production is not approved. Consequently, our study did not include the Urabe strain.

In conclusion, the incidence of aseptic meningitis after vaccination was about 1/27 of that with symptomatic natural infection, and 1/23–1/16 of that with overall natural infection. We hope a safer vaccine for children will be developed. Vaccination safety is essential but vaccine adverse effects should be discussed based on risk and benefit considerations, namely the incidence and severity of effects of the preventable natural disease. Although these data were limited for complete

consideration of benefit of vaccination, we believe we should resume MMR vaccination in Japan as well as in other countries as part of a global immunization strategy.

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施設入所高齢者と看護・介護職員のインフルエンザワクチンの接種状況と施設内流行

―北海道インフルエンザ研究―

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はじめに

北半球においては毎年冬にインフルエンザは流行し，数百万に及ぶ人々が健康被害を受ける[1]。このため，インフルエンザ対策は公衆衛生上の重要課題であるとの認識のもとに，欧米諸国では特に高齢者などのハイリスク者に対する予防接種を強力に推進している[2]。また，施設入所高齢者は，閉鎖的な環境で密接な集団生活を営んでいるため，いったんインフルエンザウイルスが施設内に持ち込まれると集団発生に結びつく可能性が高い[2]。このため，多くの国が施設入所高齢者への予防接種を勧告しており，それらの対象者への接種費用は国または社会保険で負担されている[3]。

欧米各国では1980年以降，インフルエンザワクチンの配布量が増加していたのに対し，わが国では，インフルエンザワクチンの配布量は1987年ごろから減少し，1994年には激減した[2][3]。この背景としては，1993年の公衆衛生審議会より提出された「今後の予防接種制度の在り方について」に基づき，1994年に「予防接種法および結核予防法の一部を改定する法律」が施行されたことによると考えられる[2][4]。これにより，インフルエンザは，痘瘡，コレラ，ワイル病とともに予防接種法が定める対象疾患から外れることになった。その一因としては，インフルエンザワクチンの効果を判定する研究者が，かぜとインフルエンザを混同し，「ワクチン接種者も風邪にかかるのでインフルエンザワクチンは効かない」とワクチン接種の効果を不当に過小評価したことである[4]。なかでも，前橋医師会の学童に対するインフルエンザワクチンの有効性に関する報告はインフルエンザワクチンの学童接種の見直しに大きな影響を与えた[5]。その後，見直しが行われ，2001年に予防接種法が改正され，Ⅱ類疾病という概念が確立され，対象者を65歳以上の高齢者としてインフルエンザワクチンの接種が勧奨されるようになっている[2][6]。

現在，わが国では1976年以降，幼稚園，小中学校および高等学校の園児，児童，生徒に対して行っていた社会防衛のためのインフルエンザワクチンの接種ではなく，個人の発病予防効果や重症化予防効果を期待した個人防衛の立場からの高齢者に対するインフルエンザの予防接種が行われ，その結果として社会全体の疾病の発生予防を図るという考え方になっている[2]。しかし，これだけでは不十分である。欧米では，ハイリスクの者だけではなく，医療従事者がインフルエンザに感染して，施設内に流行を持ち込む事を防ぐ観点から医療従事者に対してもワクチン接種が奨励されている[7]。

今回，我々は北海道の高齢者入所施設の入所者およびそこで働く看護・介護職員のインフルエンザワクチンの接種状況とインフルエンザ様疾患の罹患と施設内流行について，調査を行ったので報告する。

Ⅰ．対象と方法

北海道内の高齢者入所施設（老人保健施設137施設，特別養護老人ホーム254施設，養護老人ホーム57施設，軽費老人ホーム82施設，有料老人ホーム17施設）を対象に入所者とそこで働く看護・介護職員のインフルエンザワクチン接種状況

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とインフルエンザ流行期間（2002年11月から2003年3月）中のインフルエンザ様疾患の発生状況に加え，施設の特性（入所者の定員数，看護・介護職員の人数，痴呆や寝たきりの入所者や80歳以上の高齢者の人数），看護・介護職員のインフルエンザワクチン接種に対する金銭的補助について，郵送法でアンケート調査を行った。なお，寝たきりは日常生活自立度ランクBまたはCの者とした。

また，施設の特性の違いを考慮して，特別養護老人ホームに限局した分析も行った。

Ⅱ．結　　果

1．高齢者入所施設全体の調査

対象施設547施設のうち，409施設より回答が得られた（回収率74.8%）。施設の内訳は特別養護老人ホーム191施設（回収率75.2%），老人保健施設103施設（回収率75.2%），養護老人ホーム41施設（回収率71.9%），有料老人ホーム9施設（回収率52.9%），軽費老人ホーム65施設(回収率79.5%）であった。表1に入所者の定員数を示す。50人から99人の施設が58.9%で一番多く，100人から149人の施設が28.1%で続き，50人から149人の施設が87.0%を占めていた。入所者の定員数では49人以下の施設が88.5%を占めていた。表には示していないが，看護・介護職員数は9人以下が18.3%で，10～19人17.6%，20～29人20.3%，30～39人16.1%，40～49人16.1%，50～79人9.0%，80～99人0.2%，100人以上0.5%，未記入・その他1.7%であった。表2に入所者の特性を示す。認知症（痴呆）の入所者が50%以上の施設は60.9%を占めていた。寝たきりの高齢者の割合は9%以下が30.8%，70～89%が17.1%，30～49%の施設が16.6%，50～69%が15.2%と9%以下と30%から89%に二つのピークを認めた。表3に示すように，28.1%の施設で入所者にインフルエンザ様疾患の罹患を認め，8.1%の施設で入所者3人以上の連続したインフルエンザ様疾患の罹患を，9.3%の施設で入所者の5%以上にインフルエンザ様疾患の罹患を認めた。表には示していないが4.9%の施設では入所者の10%以上にインフルエンザ様疾患の罹患を認めた。

表には示していないが，看護・介護職員にインフルエンザ様疾患の罹患を認めた施設は149施設（36.4%）で，入所者にインフルエンザ様疾患の発生を認めた施設（28.1%）よりも多かった。表4に入所者と看護・介護職員のワクチン接種率を示す。入所者では接種率90%以上の施設が58.7%，70～89%の施設が21.5%で，70%以上の施設が80.2%を占めていたが，看護・介護職員のワクチン接種率は90%以上の施設が45.2%，70～89%の施設が17.1%で，70%以上の施設は62.3%にすぎなかった。また，看護・介護職員に対するワクチン接種率が9%以下の施設も11.7%認めた。看護・介護職員は，入所者に比べ，ワクチン接種率が低い施設が多かった。表5に示すように，職員のワクチン接種の費用については49.1%が接種費用を全額補助していたが，全額自己負担の施設も

表1　参加施設の入所者の定員

人　数	施設数(%)
29人以下	1.0%
30～49人	7.3%
50～99人	58.9%
100～149人	28.1%
150～199人	3.7%
200人以上	1.0%

表2　入所者の特性

	認知症（痴呆）	寝たきり（ランクB，C）	80歳以上
9%以下	13.7%	30.8%	0%
10～19%	5.1%	7.6%	2.0%
20～29%	5.6%	7.6%	1.7%
30～49%	13.0%	16.6%	6.8%
50～69%	20.3%	15.2%	30.6%
70～89%	27.9%	17.1%	53.3%
90%以上	12.7%	2.2%	5.1%
未記入・その他	1.7%	2.9%	0.5%

表3　入所者のインフルエンザ様疾患の罹患と施設内流行

	罹患	施設内流行1（連続3人以上罹患）	施設内流行2（5%以上罹患）
あ　り	28.1%	8.1%	9.3%
な　し	71.6%	89.5%	75.6%
未記入・その他	0.2%	2.4%	15.2%

表 4　入所者と看護介護職員のワクチン接種率

	入所者	看護介護職員
9％以下	1.2%	11.7%
10～19%	1.5%	4.4%
20～29%	1.0%	3.2%
30～49%	4.2%	9.0%
50～69%	11.0%	8.1%
70～89%	21.5%	17.1%
90%以上	58.7%	45.2%
未記入・その他	1.0%	1.2%

表 5　看護介護職員のワクチン接種費用

全額補助	49.1%
一部補助	18.8%
全額自己負担	31.3%
未記入・その他	0.7%

31.3%に認められた。

2. 特別養護老人ホームに限定した分析

インフルエンザ様疾患の発症が認められたのは191施設中50施設（26.2%），流行が認められた施設は17施設（8.9%）であった。

入所者のインフルエンザ様疾患の発症は，図1に示すように，ワクチン接種率30%未満の施設では50.0%，ワクチン接種率30～69%の施設では31.6%，ワクチン接種率70%以上の施設では25.0%に認め，インフルエンザ様疾患の発症がみられた施設はワクチン接種率が低い施設ほど多かった。

入所者のインフルエンザ様疾患の流行（入所者の5%以上の罹患）は，図2に示すように，ワクチン接種率30%未満の施設では40.0%，ワクチン接種率30～69%の施設では0%，ワクチン接種率70%以上の施設では10.8%に認め，インフルエンザ様疾患の発症がみられた施設はワクチン接種率が低い施設で多かった。

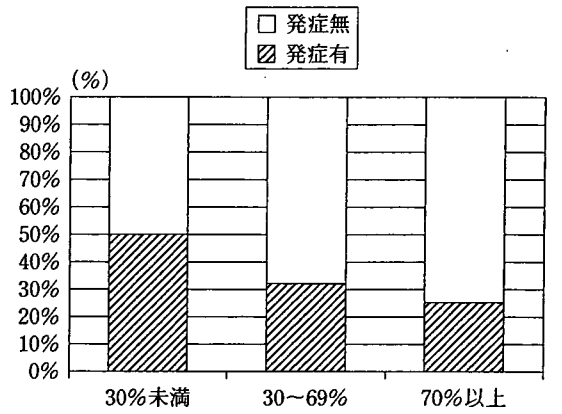
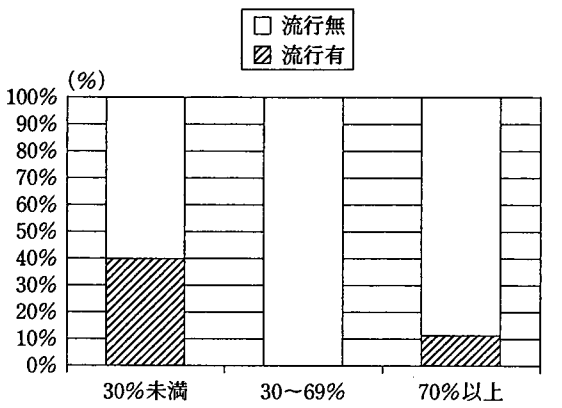


図 1　ワクチン接種率毎の入所者のインフルエンザ様疾患の発症



流行*：入所者の5%以上のインフルエンザ様疾患の罹患

図 2　ワクチン接種率毎の施設でのインフルエンザ様疾患の流行*

Ⅲ. 考　　察

1. 高齢者入所施設全体の調査

今回の調査では，北海道の全高齢者入所施設の75%の協力が得られた。入所者へのインフルエンザワクチンの接種は6割以上の施設が90%以上の入所者に対してインフルエンザワクチンの接種をおこなっており，70%から89%の入所者に対してインフルエンザワクチンの接種を行っている21.5%をあわせると，8割となった。一方，看護・介護職員のインフルエンザワクチンの接種率が90%以上の施設は5割をきっており，1割強の施設はワクチンの接種率は9%以下であった。職員のワクチン接種率については職員が施設には知らせずに個人的にワクチン接種を行っているケースは含まれていないと考えられるので，実際のワクチン接種率よりも低く見積もっている可能性も否定できないが，入所者のワクチン接種率に比べるとかなり低いといえる。今回の調査では，28%の施設で，入所者にインフルエンザ様疾患の罹患を認めた。2002/03シーズンのインフルエンザの流行株は全国的にみるとAH3型とB型の流行がみられたが，北海道の札幌市衛生研究所の報告[8]でも，A香港（A/H3N2）の初分離は2002年12月9日，ピークは第2週，B型の初分離は2003年1月11日，ピークは第10から12週というように，AH3型とB型の2つの株の流行がみられた。今回，我々が

行った調査では，2002年11月から2003年3月までのインフルエンザ様疾患の罹患をまとめて質問しており，どの型が優勢であったかなどの詳しい分析はできない。各月ごとの罹患状況を質問するようにすべきであったかもしれない。2002年度のワクチンはAソ連型：A/New Caledonia/20/99(H1N1)，A香港型：A/Panama/2007/99(H3N2)，B型：B/Shandong/7/97であり[9]，ワクチンのインフルエンザ様疾患発症予防の効果は十分期待できたと考えられ，ワクチンを接種していなければ，もっと多くの施設で入所者にインフルエンザ様疾患を認めたと考えられる。事実，今回の調査では，ワクチン接種率が高かった入所高齢者にインフルエンザ様疾患の罹患を認めた施設は28%であるのに対し，ワクチン接種率が低かった看護・介護職員にインフルエンザ様疾患の罹患を認めた施設は36%もあり，健常人である看護・介護職員にインフルエンザ様疾患の罹患を認めた施設のほうが，ハイリスク者である施設入所高齢者にインフルエンザ様疾患の罹患を認めた施設よりも多かった。高齢者入所施設全体の調査では，喉の痛み，咳，鼻水などがある39度以上の発熱をインフルエンザ様疾患の罹患と定義したため，高齢者ではその罹患を低く見積もっている可能性も否定できないが，それとは逆に，RSウイルスなどのインフルエンザ以外の疾患が混入している可能性は低いと考えられる。37度以上，38度以上，39度以上の発熱と段階的に質問したかったが，アンケート調査の回収率の低下を避ける意味で今回は39度以上の発熱だけについて調査を行った。また，今回の調査では，看護・介護職員に対してもインフルエンザ様疾患の罹患について質問しているので，前橋市医師会の学童での調査のように37度以上の発熱とするとRSウイルスなどのインフルエンザ以外の疾患が混入する[5]ため，健常人である看護・介護職員のインフルエンザ罹患に感冒の混入を避ける意味でも39度以上の発熱をインフルエンザ様疾患と定義した。入所者の5%以上に罹患を認めた施設は38施設（9.3%），10%以上に認めた施設は20施設（4.9%）もあった。施設入所高齢者はインフルエンザ様疾患に罹患すると，続発する肺炎[10]や心不全[10]などで入院する可能性が高いので，施設入所高齢者にとって，インフルエンザ様疾患の予防は大切であると考えられる。インフルエンザワクチンの接種は施設入所高齢者のインフルエンザ流行期間の入院を予防する[11]ので，禁忌などの特別な理由がない限り，施設入所高齢者にたいしてはインフルエンザワクチンを接種するように勧めるべきであろう。今回の調査では，入所者にインフルエンザ様疾患の罹患を認めた施設は，看護・介護職員にインフルエンザ様疾患の罹患を認めた施設よりも少なかった。欧米では，ハイリスクの者だけではなく，医療従事者がインフルエンザに感染して，施設内に流行を持ち込む事を防ぐ観点から医療従事者に対してもワクチン接種が奨励されている[6]のに対し，わが国ではそのような法律はなく，今後の検討課題と考えられる。職員の低いワクチン接種率の一因としては自己負担の費用の問題があると考えられる。ワクチン接種の費用が全額自己負担の施設が3割以上もあり，公費で費用を補助するなどのワクチン接種率向上のための政策の必要性が示唆された。

2. 特別養護老人ホームに限定した分析

施設の特性の違いを考慮して，特別養護老人ホームに限局した分析でも，ワクチン接種率の低い施設では入所者にインフルエンザ様疾患の罹患を認めた施設や施設内流行（入所者の5%以上がインフルエンザ様疾患に罹患）が認められた施設が多かった。以前，我々が行った特別養護老人ホーム入所者を対象におこなったインフルエンザワクチンの効果判定のためのコホート研究では，入所者に対するインフルエンザワクチン接種は入所者の入院に対して予防的に働いていた[11]。今回の調査では施設という集団を対象とした生態学的研究であり，個人レベルでのインフルエンザワクチンの有効性の検討を目的とした研究ではないが，ワクチン接種は施設でのインフルエンザ様疾患の流行に予防的に働く可能性が示唆された。高齢者施設入所者に対するインフルエンザワクチン接種は，わが国においても2001年に予防接種法が改正され，65歳以上の高齢者に対するインフルエンザワクチンの接種が勧奨されるようになっている。施設入所高齢者はワクチン接種に対する禁忌など特別な理由のない限り，ワクチン接種を行うべきであろう。

ま　と　め

今回の研究は集団を対象とした調査であり，個人の情報を集めたものではない。しかし，今回の調査の結果は入所高齢者に対するワクチン接種だけではなく，職員に対するワクチン接種もインフルエンザ様疾患の発生に対して効果があったとい

うSaitoら[12]の研究結果と矛盾しない。看護・介護職員のインフルエンザ様疾患の罹患は高齢者入所施設に，感染源を持ち込むことになる[7]ので，高齢者入所施設でのインフルエンザの流行を予防するためには入所者だけではなく，そこで働く看護・介護職員に対するワクチンの接種率を高めるための工夫が必要である。

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肺炎球菌ワクチンの公費補助を行っている全国の自治体担当者に対する聞き取り調査

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インフルエンザワクチンと肺炎球菌ワクチン

—予防医学の観点から—

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大浦麻絵　森満

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C.C.Report

高齢者には一般的に加齢に伴う呼吸機能や腎機能など各臓器の生理機能の低下が見られ、インフルエンザに罹患すると重篤化して死に至ることもあり、予防が大切です。ここでは、介護予防の視点からインフルエンザ予防の大切さを述べるとともに、ワクチン接種の重要性について解説します

高齢者をインフルエンザから守るワクチン接種
——介護予防の視点から

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高齢者のインフルエンザ予防は介護予防としても重要

2006年に介護保険制度が一部改正され、従来の介護事業に加えて介護予防事業が新設された。介護予防という概念および政策は、介護度が軽度な者をそれ以上進行させないという立場だけでなく、現在元気に自立している者を将来にわたって介護保険の適用にならないようにすることも大切な柱の1つである[1]。

●重篤化しやすい高齢者の感染

インフルエンザは、健康な成人にとっても高熱が数日間続くかなり重症の感染症であるが、通常は1週間前後で回復する。しかし65歳以上の高齢者の場合、罹患すると重篤化しやすく、致死的な感染症となることもある。

インフルエンザによる肺・循環器疾患による死亡は、0〜49歳では10万人当たり0.4〜0.6人、50歳〜64歳では7.5人であるのに対して、65歳以上では98.3人と推計されている。肺炎およびインフルエンザによる死亡の90%以上は高齢者といわれている[2]。

また、肺炎の合併率は、小児や成人において0〜7.1%であるのに対し、高齢者では8.7〜28.6%と高率になっている。これら合併症の併発は高齢者を要介護状態へと移行させる危険があり、高齢者の生活能力やその人らしさを喪失させる重大な影響をもたらすことにつながる。

●寝たきりを引き起こすことも

つまり、**図1**、**図2**に示す通り、高齢者は一般的に加齢に伴う呼吸機能、腎機能、内分泌機能など各臓器の生理機能の低下が見られる。それらを背景として、インフルエンザの