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Influenza Epidemics in a Non-Vaccinated Area

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[New Year’s first market in Maebashi] Every January 9, the market is attended by 500,000 people. Then, the influenza season comes.

[Blood sampling from schoolchildren] Blood is collected from schoolchildren biannually: before and after an epidemic. Some children, who cried when they were second graders, are now junior high school students.

Foreword

Syo Ubukata, President of the Maebashi Medical Association

I would like to offer my congratulations on the publication of Influenza Epidemics in a Non-Vaccinated Area. This reminds me of an incident seven years ago. In November 1979, a fifth grader at an elementary school had a convulsive seizure after a first dose of influenza vaccine. An adverse reaction to the vaccination was suspected, and a vaccination committee and others from the Maebashi Medical Association investigated the case and submitted the results of the investigation to the vaccine-related health hazard investigation committee in Maebashi City. The second doses of the vaccine were suspended. The committee held discussions and consulted with the council for communicable disease prevention in the Ministry of Health and Welfare. The council concluded that the seizure was not attributed to the vaccination but to genuine epilepsy. In response to the conclusion, the health hazard investigation committee in Maebashi City further scrutinized the case. The committee was dissatisfied with the conclusion drawn by the Ministry of Health and Welfare but did not submit an additional report. Instead, Maebashi City offered relief measures of its own. Since then, the influenza vaccination has not been provided in Maebashi City.

As detailed in this report, it is well known that influenza vaccines are less effective than other vaccines because influenza viruses mutate every year. The problem is not a major reason for discontinuation of vaccinations in Maebashi City. The city has raised questions about the appropriateness of administering approximately 30 doses of foreign protein vaccine to children and students in the developmental stage and using them for protection of the community. These concerns and a suspected case of an adverse reaction led to the discontinuation of the vaccination program.

It was a very difficult decision to discontinue influenza vaccinations provided in accordance with the national provisional preventive vaccination law. However, I believe that it was natural for physicians who were on the frontline of community health care and responsible for the health management of schoolchildren to take the action when the abovementioned incident occurred and that it was an appropriate action.

Since then, seven years have passed. In 1981, physicians in private practice and some public officials formed a research group on the efficacy of influenza vaccines. Physicians who were busy with everyday practice spent considerable time and effort and summarized valuable data collected for five years, leading to the publication of this report. I express my deep respect for their achievement, expect further research in the future, and hope that this report will contribute to future measures for the prevention of influenza. Finally, I gratefully extend my appreciation to the Toyota Foundation for its support.

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I. Introduction

Since the second dose of the vaccine was discontinued in November 1979, mass influenza vaccinations have not been provided in the schools at Maebashi City. Physicians who were on the frontline of the school health in Maebashi suggested that it would be beneficial for schoolchildren and students to discontinue vaccine, and the mayor of Maebashi City made decisions according to their suggestions.

The physicians' judgment was based on enthusiastic studies and discussions. Still, it required a great deal of courage, because the physicians were keenly aware of their responsibilities to schoolchildren and students. Thus, we decided to form the research group to investigate the details of influenza epidemics and continued activities for the past five years.

Our research was conducted as a part of the responsibilities of those engaged in school health, not purely for academic purposes. Large amounts of data were collected for five years, and some valuable findings were obtained. Although some data have not been fully analyzed for publication, we have decided to provide an outline of the research results obtained so far.

Our research focused on the investigation of influenza epidemics in an area without influenza vaccinations. We intended to resume vaccinations if the research demonstrated that discontinuation of mass vaccinations was inappropriate. However, the results have provided no rationale for resuming vaccinations.

In this report, we intend neither to describe the merits and demerits of influenza vaccines nor to investigate in detail the efficacy of vaccines in preventing infection and disease onset. However, we are very interested in whether the mass vaccination of schoolchildren and students is useful in preventing influenza epidemics. We believe that it would be just time to review compulsory mass vaccinations of schoolchildren and students. Hopefully, our result could be useful as reference materials for the review.

II. Survey

1. Background and objective

It has been about 30 years since an inactivated influenza vaccine was first put to practical use, and 23 years have passed since the mass vaccination of schoolchildren was started as a special prevention program in Japan. It has been 10 years since it was designated as a statutory vaccination after revisions to the Preventive Vaccination Law in 1976.

The Japanese policy on the influenza vaccination program was originally developed from the viewpoint of protection of the community. The program aimed to suppress local epidemics by the mass vaccination of schoolchildren, although influenza vaccine was known to have limited efficacy for personal protection. The program was based on the assumption that an epidemic first occurred among schoolchildren and then expanded in local communities. With the exception of Japan, there were no countries in the world where schoolchildren were forced to receive mass influenza vaccinations under such a policy.

At that time, the vaccination policy was somewhat convincing, and the judgment on its introduction appeared to be valid. However, circumstances changed over time, and it cannot be helped that past experience becomes obsolete. Under such circumstances, we believed it necessary to review the following issues.

1) Role of schoolchildren in influenza epidemics

Our society has changed substantially over a period of 30 years since the vaccine was available for the first time. Advances in transportation and increased economic activities are associated with a rapid increase in the field of activities of people. This accelerates the spread of many communicable diseases. It is increasingly common for the same strain of influenza virus to spread across the country. This suggests that adults play a greater role in the spread of the virus and that the relative role of schoolchildren is decreased.

2) Epidemic conditions

It has been 30 years since the first vaccine was put to practical use, and it has been a decade since vaccinations became legally required. Still, epidemics occur repeatedly. How should we interpret these conditions? It may be wrong to continue the current practice without evidence to support the assumption that the vaccination of schoolchildren helps protect communities from influenza.

3) Selection of vaccinees

As is well known, severe forms of influenza are uncommon in schoolchildren. Persons at a risk of a poor outcome from influenza are limited to older individuals 60 years of age or older and immune-compromised persons with some disease. Despite this, the current program offers vaccinations to healthy schoolchildren, not to high-risk individuals. Is it appropriate?

4) Advances in antibiotics

The majority of deaths from influenza are attributed to pneumonia, mostly bacterial pneumonia, which is caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. It is evident that the condition can be treated with antibiotics.

5) Advances in immunology

It is now known that secretory IgA antibodies play a major role in the protection against infectious diseases such as influenza that cause mucous membrane lesions but no viremia. It is found that the production of IgA antibodies is induced by infection but not by inactivated vaccine.

These five issues were not expected at the start of the vaccination program. Thus, we should use currently available data to review the program rather than cling to an old way of thinking.

Maebashi City discontinued mass vaccinations according to the Maebashi Medical Association's recommendation, and we formed a research group to conduct this survey. The background and history of the initiatives are described below.

After the Preventive Vaccinations Law was enacted in 1948, the Maebashi Medical Association fully and actively cooperated with Maebashi City in the vaccination program. The president of the Maebashi Medical Association and the Maebashi mayor concluded a vaccination service agreement in 1969, and the medical association established a vaccination committee in 1972. Since then, members of the medical association and city officials in charge of vaccinations always attended the committee meeting. One of the important tasks of the committee was to determine specific procedures to ensure smooth vaccinations in accordance with the Preventive Vaccinations Law. Another important task was to thoroughly examine notifications sent by the Ministry of Health and Welfare via the prefecture, discuss ways to ensure that vaccinees benefit most from safe vaccinations, and provide its opinions to board members (executives of the medical association). As needed, a responsible board member from the medical association often asked the head or a responsible person of health centers or other vaccination-related institutions to participate in the discussion. Thus, the medical association always closely cooperated with administrative agencies and exercised leadership as an expert. The city highly evaluated the significance and quickly took action. The two parties enjoyed such a relationship for years.

A few unique examples of past activities in Maebashi City are described below. In December 1974, a fatal accident led to the discontinuation of the DTP vaccine. When receiving a notification of resumption from the Ministry of Health and Welfare in April 1975, the committee reviewed the case and decided not to resume vaccinations. However, the committee asked some members of the medical association to conduct a survey on pertussis in December 1975 and resumed a second phase of the DTP vaccine on the basis of the survey results in February 1976; Maebashi city resumed it earlier than any other district in Japan.

When the measles vaccination was designated as a statutory vaccination in 1978, the city decided to cover all costs for vaccinees 1 to 6 years of age in December 1978. The city started an extensive survey on adverse reactions to the measles vaccine in February 1979 and submitted the results to a vaccination study group from the Ministry of Health and Welfare. With the eradication of smallpox being declared in 1980, physicians suggested the initiation of a measles eradication campaign, and the president of the medical association submitted a written request to the mayor. Receiving the request, the city officially started the measles eradication campaign, which is ongoing.

In 1979, to ensure that all individuals were vaccinated, the following procedures were adopted. The eligibility for the rubella vaccine was changed from ninth graders to eighth graders. To ensure that they acquired immunity, antibody titer testing was performed on all eighth graders before the vaccination, and those with negative tests were vaccinated. Antibody titer testing was performed again when the vaccinees became ninth graders, and those with negative tests were vaccinated again.

For influenza, revisions to the Preventive Vaccination Law in 1976 were followed by initiation of statutory mass vaccinations for schoolchildren, and the medical association actively cooperated with the city. Despite our considerable time and effort, influenza epidemics were an annual event.

In July 1977, Dr. Shuzo Yugami, Dr. Shigeo Kuwashima, Dr. Hideaki Yagi, and others (vaccination committee members at that time and some remain as group members) investigated the relationship between the vaccination rate and the incidence of the influenza-like common cold in schools and gave a presentation titled “Efficacy of Influenza Vaccination” at the Gunma Meeting of the Japan Pediatric Society. They argued that vaccine efficacy was questionable and that it was time to perform a reexamination (see Appendix 1).

As shown in Table 1, the Maebashi Medical Association has invited experts and researchers to convene workshops up to three times annually since 1975 with the aim of better understanding vaccinations as a whole and obtaining opinions on the evaluation of the influenza vaccine, in particular. Their opinions differed slightly: some said that vaccinations would be better than nothing at all, and other said that you should not expect much of it. Except for Dr. Hideo Fukumi, none of them highly evaluated vaccinations. However, Dr. Isao Ebisawa, a world-class virologist and expert in vaccines, asserted that the mass vaccination for schoolchildren in Japan was not effective and criticized the Japanese policy on influenza vaccination.

Under such circumstances, after reporting its decision to the Gunma Council, Maebashi City discontinued vaccinations at childcare centers and kindergartens and then discontinued vaccinations in high schools in 1979. The former decision was made primarily because the risk of adverse reactions outweighed the potential efficacy. The latter decision was made because the efficacy was not evident, because students in this age group should have physical strength enough to get over influenza, and because vaccinations were too great a burden on school physicians. The city believed that those who definitely want to receive the vaccine may do so on a voluntary basis.

Table 1. List of Vaccination Workshops Hosted by the Maebashi Medical Association.

Date			
1975.7.10	Munehiro Hirayama	Professor at the Department of Maternal and Child Health, Faculty of Medicine, the University of Tokyo	Recent trends in vaccination
1976.5.11	Mikio Kimura	Professor at the Department of Pediatrics, Tokai University School of Medicine	Rubella
1976.7.14	Takeo Kuroyanagi	Professor at the First Department of Internal Medicine, Saitama Medical School	Immunology for daily clinical practice
1976.10.14	Haruo Mizuhara	Professor at the Department of Pediatrics, St. Marianna University School of Medicine	Pertussis
1977.11.10	Isao Ebisawa	The Institute of Medical Science, the University of Tokyo	Influenza vaccination[1]
1978.6.8	Munehiro Hirayama	Professor at the Department of Maternal and Child Health, Faculty of Medicine, the University of Tokyo	Vaccination for the future[2]
1978.11.21	Hiromichi Mizutani	Leader at the Virus Laboratory, Kanto Teishin Hospital	Influenza vaccine[3]
1980.9.12	Hideo Fukumi	Former Director at the National Institute of Infectious Diseases	Influenza vaccine[4]
1980.11.18	Yoshiomi Okuno	Professor Emeritus at Osaka University (Former Director at the Research Institute for Microbial Diseases, Osaka University)	New vaccine—particularly vaccine against viral disease
1981.6.10	Kouichi Yamanishi	Associate Professor at the Research Institute for Microbial Diseases, Osaka University	Mumps live vaccine[5]
1981.10.14	Junichi Yata	Professor at the Department of Pediatrics, Tokyo Medical and Dental University	New basic immunology (part 1)[6]
1981.11.25	Junichi Yata	Professor at the Department of Pediatrics, Tokyo Medical and Dental University	New basic immunology (part 2)[7]
1983.12.8	Nobuhisa Yamane	Department of Clinical Laboratory, Tohoku University Hospital	Limitations and future perspectives of influenza virus vaccine[8]

Note: Of the lectures listed above, those in 1977 and later were recorded in the Maebashi Medical Association Medical Lecture Records edited and issued by the Maebashi Medical Association. The numeral to the right of the title indicates the volume number of records as described below. It should be noted that each speaker's evaluation of the influenza vaccine is based on his opinion provided during the question and answer session after his lecture if influenza vaccine is not mentioned in the lecture record.

1) Issue for fiscal 1977, pages 75–104
2) Issue for fiscal 1978 (Volume 2), pages 219–237
3) Issue for fiscal 1978 (Volume 2), pages 239–251
4) Issue for fiscal 1980 (Volume 4), pages 237–254
5) Issue for fiscal 1981 (Volume 5), pages 63–81
6) Issue for fiscal 1981 (Volume 5), pages 155–178
7) Issue for fiscal 1981 (Volume 5), pages 179–198
8) Issue for fiscal 1983 (Volume 7), pages 257–277

In November 1979, after the first dose of the vaccine in elementary and junior high schools, a boy in the fifth grade of an elementary school experienced the adverse reaction of repeated convulsive seizures, which started on the night after the vaccination. At that time, newspapers reported the mass occurrence of collective adverse reactions in Hokkaido and a fatal accident in Niigata Prefecture. This led to the discontinuation of the second and later doses of the vaccine (see Appendix 2).

In October 1980, just before the scheduled influenza vaccination, the president of the medical association convened a vaccination committee to discuss whether or not to resume vaccinations.

After the discussion, Dr. Touichi Takahashi, the head of the committee (group member) submitted a report to Mr. Yutaka Yamashita, then president of the medical association, stating that there was no justification or need for altering the previous decision—discontinuation of influenza vaccinations because of the following reasons: the circumstances did not change appreciably compared with those at discontinuation of vaccinations in the previous year, there was a lack of new evidence against our view (the efficacy of the influenza vaccine was insufficient), there was no evidence of a higher incidence of influenza in kindergartens and childcare centers not participating in the vaccination program for years in Maebashi City, there was no evidence that discontinuation of the previous year increased the incidence of influenza in Maebashi City, and the incidence of influenza was not high in Annaka City and a part of Agatsuma-gun in which the influenza vaccination was discontinued for long. Following the report, the board members of the medical association also carefully reviewed the case and sent a written recommendation and its reasons to the Maebashi mayor, stating that it was appropriate not to provide mass influenza vaccinations to schoolchildren in the previous and current fiscal years. Since then, similar processes have been repeated, and vaccinations have not resumed.

After deciding to discontinue vaccinations, the committee wondered whether it would be appropriate to permanently discontinue influenza vaccinations and whether the discontinuation would result in a severe epidemic. Some suggested subsequent epidemics should be surveyed to demonstrate that the committee's judgment was appropriate. The survey should be useful in predicting epidemics and developing measures for the control of epidemics without vaccinations.

All members agreed with the suggestion. However, the vaccination committee was not able to perform the activities on its own and thus formed a separate research group. The vaccination committee of the medical association at that time asked others for cooperation, including school physicians approving the survey, persons related to elementary and junior high schools participating in the mass vaccination program, personnel at the municipal board of education, and municipal, prefectural, and university officials who were actually involved or interested in local control of epidemic diseases. Thus, the research group was organized. The first group meeting was held in April 1981. The group was named the Research Group on the Efficacy of Influenza Vaccines (commonly known as the research group for the study of influenza), and Dr. Shuzo Yugami was selected as the director.

With the background and history in mind, group activities were started. We committed ourselves to the survey because the efficacy of the vaccine was largely questionable despite a long history of mass vaccinations of schoolchildren, because there was a lack of empirical evaluations to answer such questions, and because the existing situation did not allow us to resume vaccinations for justifiable reasons.

2. Subjects and methods

A. Subjects

The absentee survey involved 25,000 to 26,000 children enrolled in all municipal elementary schools in Maebashi City, including 36 schools in fiscal 1981, 37 schools in fiscal 1982, 38 schools in fiscal 1983, and 39 schools in fiscal 1984 to 1985 (the number of children differed slightly depending on the fiscal year). Most figures described below are presented on a school year basis. The fiscal year runs from April to March of the following year.

Among the elementary schools described above, five schools were selected as seroepidemiological survey-designated schools. HI antibody titers were measured in a total of approximately 600 persons (second graders of these schools in fiscal 1981) over a period of five years. The location of the five designated schools in Maebashi City is shown in Figure 1. Elementary schools other than the designated schools are indicated with small circles. These five schools were selected with consideration of geographical conditions in the city and represented the environmental features of each region of the city as described below. Shikishima Elementary School was a medium-sized school enrolling about 700 children in an old area. Katsuyama Elementary School was a medium-sized school in a rural area in which homebuilding is active. Ootone Elementary School was a medium-sized school in a new area with relatively old apartment complexes (the school was initially a large school enrolling more than 1000 children but became a medium-sized one because of modification of the school district). Aramaki Elementary School was a medium-sized school in a new residential area near the Faculty of Education, Gunma University. Utsuboi Elementary School was a small school enrolling about 300 children in a purely rural area.

It should be noted that Maebashi City, the prefectural capital, is located in the central-south area of Gunma Prefecture with an area of approximately 147 km^2 and a population of approximately 270,000. It is located at the foot of Mount Akagi (northeast). Mount Haruna is located to the northwest of the city, and the Tone River runs through the west side of the city. The east and south areas are a part of the Kanto Plain. The weather in winter is characterized by continuous sunny days and northwest, dry, strong winds, which are well known as the “Dry Winds of Joshu” or “Winds from Mount Akagi.” The weather in summer is characterized by an inland climate and many hot, muggy days due to the strong sunshine. The city is the most thunder-prone area in Japan. The monthly mean temperature is highest at 25.5°C in August and lowest at 2.6°C in January. The annual mean humidity is as low as 68% (source: the *Gunma Prefecture Encyclopedia* published by Jomo Shimbun, Inc.).

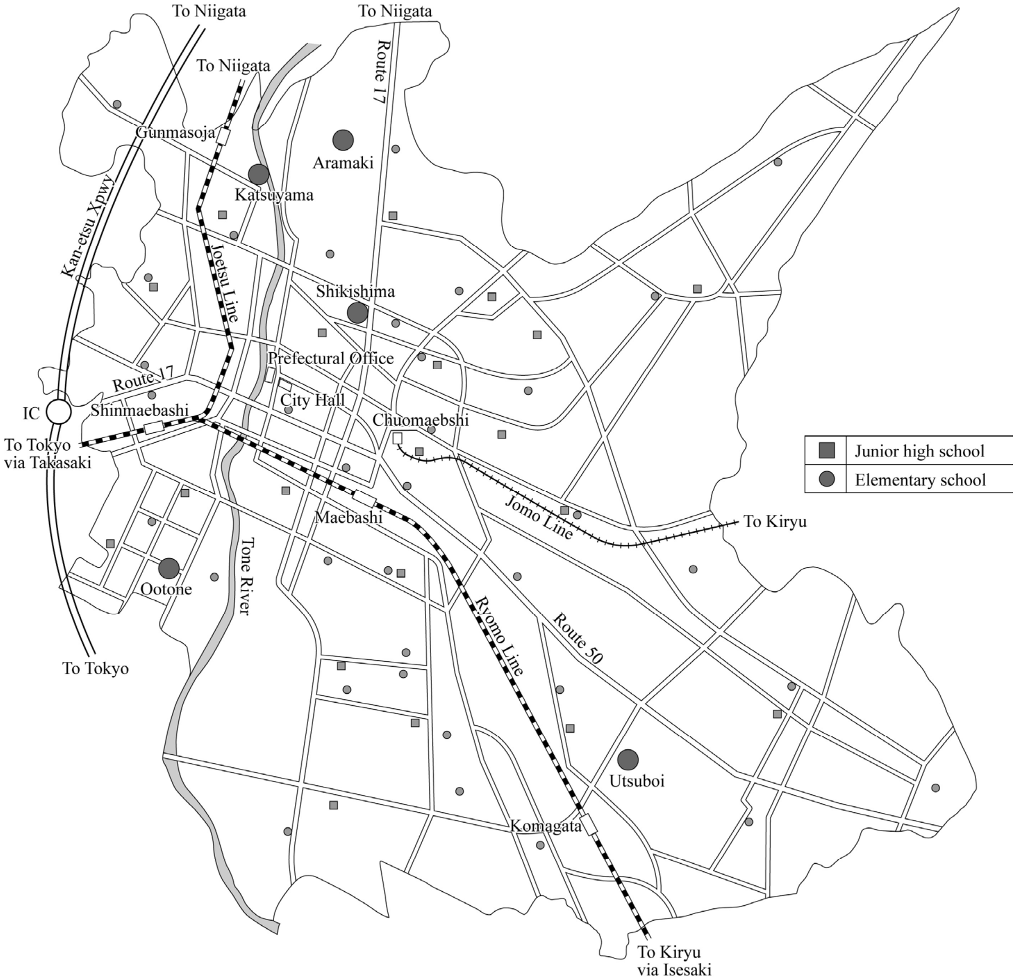


Figure 1. Location of the Five Designated Schools in Maebashi City.
●Designated schools for HI antibody titer testing

B. Methods

1) Survey involving all elementary and junior high schools in the city

(i) Survey on the daily number of absentees during the school term

(Hereafter abbreviated as the "survey on the daily number of absentees")

In January 1981, we started a survey on the daily number of absentees during the school term throughout the year at all municipal elementary and junior high schools, excluding schools for children with disabilities. However, the survey excluded long-term absentees with chronic diseases or specific reasons, absentees with trauma, and those on bereavement leave. Each school was given a standardized survey form and sent it back to the board of education every month for summarization.

This report focuses on the absentees at elementary schools but takes the absentees at junior high schools into consideration for assessment of the conditions. This is partly because elementary schoolchildren with a temperature of 38°C or more were likely to be absent from school and because differences in other conditions for absences seemed to be relatively small among schools and individuals.

The survey results were used to calculate the daily rate of absentees (hereby after reffered to the absentee rate). When the rate in all municipal schools and the school-specific rate were calculated during class closures, the parameter was calculated by subtracting the number of enrolled children in closed classes from the total number of enrolled children.

(ii) Class closure survey

The preexisting Report on the Onset of Influenza-like Illness was used to examine class closures (Table 2). For fiscal 1980 (January to March 1981) when the influenza A/H_1N_1 (A/USSR) epidemic occurred, however, a somewhat different form was used to evaluate the effect of class closures, which is described in the next chapter.

Table 2. Report on the Onset of Influenza-like Illness (example).

<table>
<tr><td colspan="6">Report on the Onset of Influenza-like Illness</td></tr>
<tr><td>Reporter</td><td colspan="5">Occupation and name: Nursing teacher, Masako Kofuna</td></tr>
<tr><td>Date of communication</td><td>Friday, December 6, 1985</td><td>AM
PM</td><td colspan="3">1:00</td></tr>
<tr><td>School</td><td colspan="2">Municipal Katsuyama Elementary School in Maebashi</td><td colspan="2">Principal</td><td>Takao Watanuki</td></tr>
<tr><td colspan="2">Number of classes</td><td colspan="2">Number of enrolled children</td><td colspan="2">Total number of absentees</td></tr>
<tr><td colspan="2">18</td><td colspan="2">611</td><td colspan="2">46</td></tr>
<tr><td rowspan="2">Grade/class closure</td><td>Grade / Class</td><td>Number of enrolled children</td><td>Number of absentees</td><td>Number of persons with fever (37°C or more)</td><td>Closure period</td></tr>
<tr><td>Grade 5,
Class 1
Class 3</td><td>31
31</td><td>8
8</td><td>1
4</td><td>December 7 to 10</td></tr>
<tr><td colspan="3">Closure of grade/class is a new or repeated one.</td><td colspan="3">As a school, closure of grade/class is a new or repeated one.</td></tr>
<tr><td>Course of symptoms</td><td colspan="5">Cough: severe, mild
General malaise: severe, mild
Fever: 38°C to 40°C
Nasopharynx: nasal discharge
Headache: severe, mild
Low back pain or arthralgia: severe, mild
Others</td></tr>
<tr><td>Vaccination status</td><td colspan="5">School as a whole Not performed at all
School as a whole Performed 1st dose (date) 2nd dose (date)
School as whole Date %</td></tr>
<tr><td>School physician</td><td colspan="5">Shunya Nomachi, Masao Todokoro</td></tr>
<tr><td>Sample collection</td><td colspan="5">None (sixth graders: persons with fever and Grade 6 Class 3, throat culture performed for 5 days)</td></tr>
<tr><td>Others remarks</td><td colspan="5">Grade 5, Class 1 5 days 13 children absent
Grade 5, Class 3 5 days 4 children absent</td></tr>
</table>

2) Survey and testing in designated schools

(i) Absentee survey by individual

When children of the grade enrolled in the HI antibody titer testing were absent at any time of year, their parents were asked to submit the Absentee Report as shown in Table 3 after entering the following information: the number of days absent, the presence or absence of fever, highest temperature, the presence or absence of cough and diarrhea and severity, and diagnosis if informed by the physician. The number of days absent was one when a child was absent only for one day. When a child was ill on Sundays and holidays, those days were also included in the number of days absent. Whenever the form was submitted, all entries were checked by a nursing teacher. A blue form was used for boys, and a pink form was used for girls to facilitate subsequent data analysis. Calculation of the number of absentees and analysis of the incidence by antibody titer during epidemic periods were based on this survey. Details are described in each section.

Table 3. Absentee Report by Individual.
(A blue form and a pink form were used for boys and girls, respectively.)

To parents

Principal of elementary school

I ask you to complete and submit the following Absentee Report, which is used as material for examination of the epidemic of common colds or influenza-like illnesses and the development of preventive measures against epidemics.

Absentee Report

Grade Class Number	Name of child		Name of parents	
Circle appropriate items and enter details in parentheses. Fever: Yes / No (highest temperature °C) Cough: Yes / No (mild, moderate, severe) Diarrhea: Yes / No (about times a day) Other significant symptoms: ( ) Diagnosis if reported by your physician ( ) Family member with fever: Yes / No └Order of onset A: Fever developed first in a family member. B: Fever developed first in the child.				

(ii) Influenza HI antibody titer testing

In fiscal 1981 and thereafter, blood was collected from approximately 600 second graders in five designated schools in November and May, that is, before and after annual epidemics (every six months, twice a year) to measure the HI antibody titer. When these children became sixth graders, however, the second blood sampling was performed in March 1986, and the five-year project was completed. It should be stressed that the testing was repeated with the same group of children over a period of five years.

A part of the sera was stored frozen in a freezer to measure other strains, make measurements by other test methods, or perform other analyses as needed. However, this report describes the study results primarily on the basis of HI antibody titers determined during each epidemic period with the use of vaccine strains for the year.

The HI test used for the measurement of antibody titers was based on a microtiter method.

The details of the method are not described here because it is extensively used. All HI tests were performed at the prefectural institute for public health.

(iii) Supplementary tests other than influenza HI antibody titer testing

A part of the sera collected every November was used to perform tests that appeared useful for the health management of children, and each of them was informed of the results. Table 4 shows a list of tests performed in each fiscal year. A few tests were summarized, analyzed, and reported at the Gunma Meeting of the Japan Pediatric Society or the Gunma Obesity Seminar but are not described in this report because those tests are not the major theme of this report.

Table 4. Supplementary Tests Other Than Influenza HI Antibody Titer Testing.

Fiscal year	Test
Fiscal 1981	Hemoglobin content and rubella antibody titer testing
Fiscal 1982	Total cholesterol testing
Fiscal 1983	Mumps HI antibody titer testing
Fiscal 1984	Hemoglobin content testing
Fiscal 1985	Hemoglobin content and total protein testing

The decision on whether to report the results of influenza HI antibody titer testing to individuals was at the discretion of the school physician of each school. At most schools, school physicians reported and explained the distribution of antibody titers at the school level together with epidemic situations at a meeting of the school health committee or the PTA for the grade. This provided a good opportunity to better understand influenza. However, what interested and pleased more were the results of these supplementary tests. School physicians were enthusiastic about using a school health consultation system and offering personal consultations. Blood was collected from a very high proportion of children, except those with special physical conditions. It should be stressed that such a high proportion was attributed to the supplementary tests and enthusiastic activities of school physicians.

(iv) Detection of influenza virus

Soon after the start of the survey, some planned to detect viruses in throat swab specimens of children who underwent HI antibody titer testing during a specific window of the epidemic period. During the epidemic period, however, school physicians were busy in daily clinical practice and did not have enough time to go to school. In addition, there was no way to transport samples quickly and smoothly to the institute for public health, a testing institute, which precluded the implementation of the plan at all designated schools.

In fiscal 1983, at Utsuboi Elementary School, the testing was performed with all children who had blood collected twice: early in the epidemic period and after the peak. Unfortunately, viruses could not be detected at that time.

A second attempt was made at Katsuyama Elementary School, a designated school, in fiscal 1985 to detect the influenza virus in throat swab specimens of all children in a class (sixth graders) who had blood collected early in the A/H_3N_2 (A/Hong Kong) epidemic period from November to December 1985. The testing was successful and produced interesting findings. We will repeat the same survey to analyze more samples and present conclusions in due time.

3. Results

A. Influenza epidemics in terms of the absentee rate in elementary schools in the city

1) Methods

The analysis was based on the survey on the daily number of absentees and the class closure survey described in the previous chapter. The Influenza-like Illness Surveillance Report by the Gunma Medical Association, the Epidemic Control Information by the Ministry of Health and Welfare, and curves showing the weekly number of patients with influenza-like illness across Japan were used for comparison.

2) Survey results

(i) Epidemic curve on the basis of the absentee rate

Figure 2 graphically shows the change in the absentee rate at all elementary schools in the city associated with seven epidemics occurring from fiscal 1980 to fiscal 1985 (over a period of approximately five years from January 1981 to December 1985).

An epidemic of a communicable disease was empirically suspected when the absentee rate was 2% or more for at least three consecutive days and tended to increase gradually. No epidemics occurred when the absentee rate was 2% or less. The value of 2% slightly exceeded the mean rate of absentees during no-epidemic periods plus twice the standard deviation. A rate of absentees higher than 5% was definitely associated with influenza. The criteria were not always applicable to the city as a whole when an epidemic was limited to some schools.

Needless to say, it is obvious that the absenteeism rate in this context does not exclusively reflect patients with influenza. Nevertheless, many absentees had influenza clinically when the absentee curve had a high bell-shaped appearance. (The proportion is about 60% on the basis of the change in HI antibody titer, and this is described later.) Thus, the curve appears to represent an epidemic curve for influenza and is called an epidemic curve hereafter.

The virus strain circulating during each epidemic period is indicated to the right side of the peak of the curve. A horizontal line is drawn at 2% in each figure to determine the epidemic period from the distance between intersections of the line and the absentee curve. The vertical line drawn between December and January separates years. One week before and after the line are winter holidays, and the curve is discontinuous during the time period.

A bar chart of the daily number of closed classes is superimposed on the figure. However, the heights of charts of the absentee rate and the number of closed classes are determined arbitrarily. The ratio of the number of persons is about 1:1.5. Here, importance is placed on the evaluation of the value as a measure for comparison of epidemic patterns.

Each absentee curve in the figure represents a total of approximately 26,000 children enrolled in 36 to 39 elementary schools in the city. Thus, these curves should be considered a sum of absentee curves of individual elementary schools that indicate a variety of epidemic periods, durations, and patterns. For example, a bell-shaped curve with a short epidemic period and a high peak in the figure indicates that an epidemic occurred simultaneously at elementary schools in the city. In contrast, a curve characterized by a long epidemic period and a single broad peak or multiple low peaks indicates that epidemics at individual elementary schools showed a similar trend or epidemics occurred at substantially different times.

With these conventions in mind, the features of graphically presented epidemics in fiscal years are described below. The figures of the 1981 A/H_1N_1 (A/USSR) epidemic, the 1982 influenza B epidemic, and the 1983 A/H_3N_2 (A/Hong Kong) epidemic show a symmetric bell-shaped curve with a center peak, or a typical pattern of epidemic curves.

There were small A/H_3N_2 epidemics in March 1982. HI antibody titer testing was performed at five designated schools for influenza HI antibody titer testing (hereafter simply referred to as designated schools), and A/H_3N_2 epidemics were identified at two of the five schools during this period. Analysis of the absenteeism curves for all elementary schools in the city suggested that epidemics probably occur at 14 of the 37 schools. The curve in the figure graphically represents 14 schools as a whole.

The A/H_1N_1 epidemic starting in December 1983 extended into the winter holidays and continued until March 1984 as indicated by a broad plateau. A peak appeared to occur at the end of January, but the highest rate of absentees was less than 5%. According to reports by medical institutions at that time, influenza-like illness was not particularly frequent, and the conditions were characterized by a mix of influenza-like illness and epidemic vomiting. Epidemic curves of individual schools differ substantially with respect to the epidemic period, and uniformly have low peaks. Influenza epidemics appeared to end in mid February. In such epidemics, it is impossible to determine the epidemic period according to the criterion of 2% absentee. The winter was characterized by a somewhat lower mean temperature than usual, more snow days than usual, and many humid days. The relatively small epidemic may be partly explained by the weather.

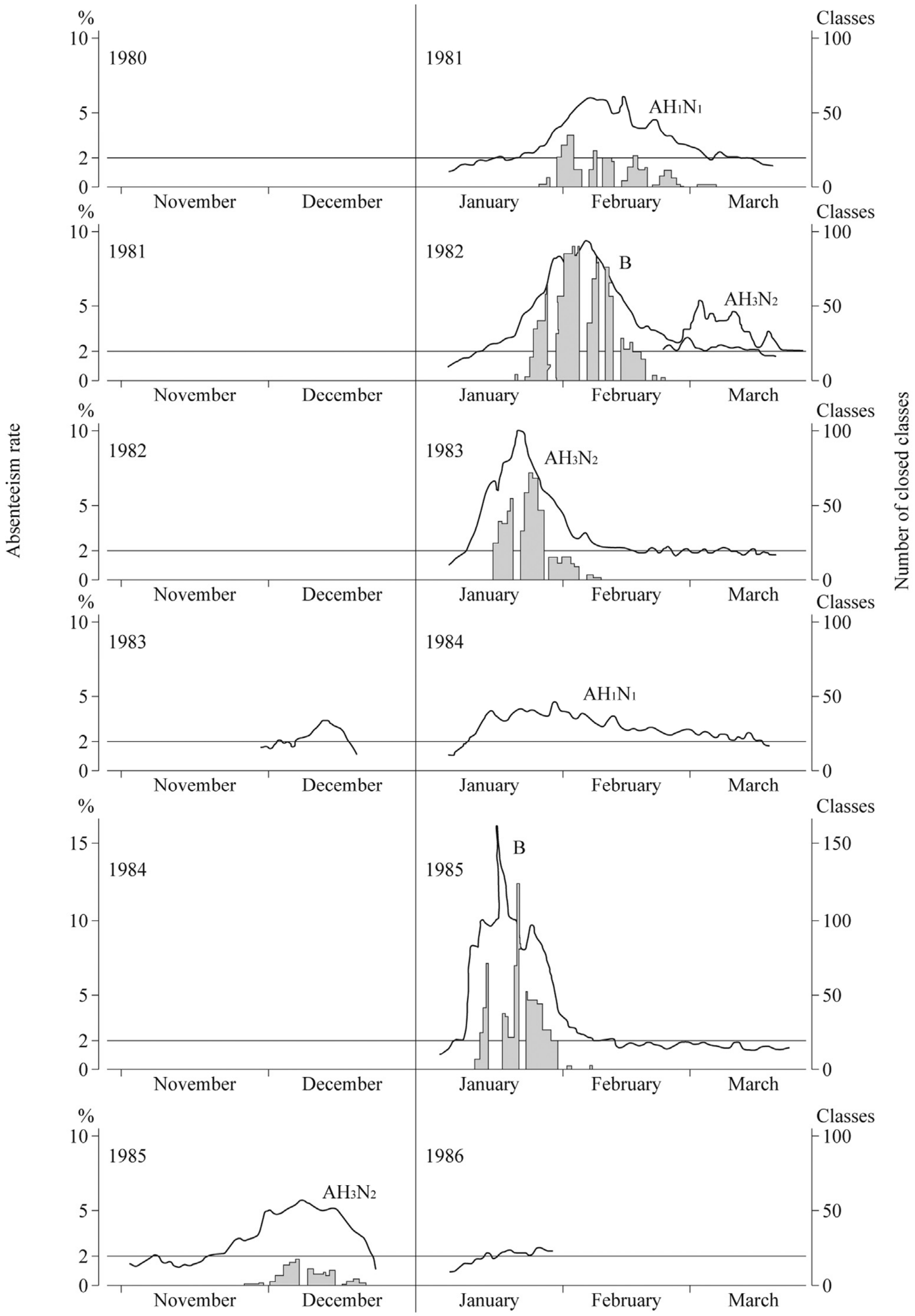


Figure 2. Influenza Epidemics in Elementary Schools in Maebashi City.

The Influenza B epidemic curve in 1985 was characterized by a rapid increase in the absentee rate, a high peak, a rapid decrease in the absentee rate, and a short epidemic period, indicating an explosive epidemic course.

In addition, an epidemic started as early as mid November in 1985. The epidemic strain was the A/H_3N_2 virus. The epidemic peaked on December 10 or so. The front and the tail of the epidemic curve were asymmetric, and the epidemic ended in an abortive manner just before the winter holidays. After the turn of the year, the absenteeism rate was 2% or more at seven or eight schools, suggesting some sort of epidemic. It remains unclear whether these were related to influenza or not. At any rate, it is certain that epidemic curves on the basis of the absenteeism rate are substantially influenced by the winter holidays.

Finally, an analysis of the epidemic curves as a whole showed that major epidemics of the A/H_1N_1, type B, and A/H_3N_2 viruses occurred in this order twice. Epidemics started earlier year after year. In fiscal 1985, the last year of the observation period, an epidemic started in November (before the winter holidays). This feature cannot be generalized but it is an interesting phenomenon.

Incidentally, Daruma-ichi, a famous New Year's first market, is opened on January 9 in Maebashi City. Although the day is usually a very cold day characterized by a famous local wind called Karakkaze, the market is said to be attended by approximately 400,000 persons a day. The number is 1.5 times the population of the city. The market is so crowded with people coming from neighboring towns and standing shoulder to shoulder that they have no choice but to come and go along with the flow of the crowd while hearing *daruma* vendors hawking their wares. Elementary schoolchildren are not an exception. As soon as school finishes, they dash to the New Year's first market. After that, many schools give children an assignment to write a report or draw a picture. Thus, schools appear to encourage children to go to the New Year's first market. In fiscal 1984 and earlier, some often suggested at the group meeting that elementary schoolchildren should not be allowed to participate in the New Year's first market, an amplifier of influenza. It is conceivable that the market plays a role in inner-city epidemics under certain conditions.

It is time to return from the digression. As shown in the figures, the profile of the daily number of closed classes appears to be roughly parallel to the absentee curve, a relative measure of the epidemic size. If the epidemic size is estimated from the absentee rate, however, the number of closed classes tends to be extremely large when the epidemic size is large and close to zero when the epidemic size is small. Thus, the epidemic size and pattern on the basis of class closure should have large errors. This procedure, of course, cannot be used to determine the epidemic period.

(ii) Class closure survey in fiscal 1980

This survey was conducted in elementary schools during the A/H_1N_1 epidemic period from January to March 1981. The objective of the survey was to establish the basis for estimating the number of absentees during class closures in order to calculate the number of absentees described in the next section. Another objective was to elucidate the class closure conditions in Maebashi City.

The survey results are shown in Table 5. The total number of closed classes was 106, and the most common number of days of class closure was 3 days (51 classes, 48.1%), followed by 5 days and 4 days (about 20% for both). The mean number of days of class closure was 3.9 days, or about 4 days.

The mean number of enrolled children per class was 37.7 children, or approximately 38. The mean number of absentees on the day before class closure was 9.5, which accounted for 25.2% of the mean number of enrolled children. The mean number of absentees when classes resumed was 3.4, which accounted for 9.0% of the mean number of enrolled children.

Table 5. Class Closure during the A/H_1N_1 Epidemic Period from January to March 1981 (School Year 1980).

Number of days of class closure*	Class composition			Number of absentees on the day before class closure			Number of absentees on resumption of classes			Decrease in the number of absentees before and after closure (%)	Number of classes closed again
	Number of classes	Total number of enrolled children	Mean number of absentees per class	Total	Mean number of absentees per class	%	Total	Mean number of absentees per class	%		
2	1	37	37	10	10	27.0	12	12	32.4	+20	1
3	51	1,939	38.0	435	8.5	22.4	221	4.3	11.4	−49.2	2
4	21	774	36.9	217	10.3	28.0	45	2.1	5.8	−79.3	0
5	24	875	36.5	239	10.0	27.3	56	2.3	6.4	−76.6	0
6	9	367	40.8	107	11.9	29.2	22	2.4	6.0	−79.4	0
School closure	22	815	37.1	137	6.2	16.8	73	3.3	9.0	−46.7	0

*The number of days of class closure includes Sundays and holidays. School closures occurred at an elementary school (Aramaki Elementary School), and the mean number of days of class closure per class was 5.4 days.

Maebashi City instructed schools to close classes for 5 days or more if the absentee rate in class exceeded 20% during the influenza epidemic period. However, these figures showed that the actual values were 25% and 4 days. The figures in this table suggest that class closure for 4 days or more appeared to be effective in decreasing absentees by nearly 80%.

However, a subsequent survey demonstrates that these figures are not enough to evaluate the effectiveness of class closures, and the limitation was frequently discussed at subsequent group meetings. The group members reached the consensus that it was necessary to develop a new survey plan to address this problem.

On the basis of those figures, the total number of absentees during class closure was estimated simply by the following formula: $(9.5 + 3.4) \times 3.9 \div 2 = 25.2$ (persons). Thus, the total number per class closure was estimated at 25 children. This value was used for a period of five years because the criteria for class closure at elementary schools in Maebashi City remained unchanged and because school physicians found no substantial change in the actual conditions.

The actual number slightly differed according to the epidemic, and a more accurate estimate could be obtained by using questionnaires and investigating the incidence during closures. Given the parameter size, however, a small error is unlikely to substantially affect the estimate.

Table 6. Absentees at All Elementary Schools in Maebashi City during Influenza Epidemic Periods.

School year		1980	1981	1982	1983	1984	1985
Epidemic season Epidemic strain		Jan to Mar 1981 A/H_1N_1	Jan to Mar 1982 B, A/H_3N_2	Jan to Mar 1983 A/H_3N_2	Dec 1983 to Mar 1984 A/H_1N_1	Dec 1984 to Feb 1985 B	Nov to Dec 1985 A/H_3N_2
Epidemic period (Note 1)		Jan 19 to Mar 16	Jan 16 to Mar 24	Jan 12 to Feb 17	Dec 12 to Mar 26	Jan 10 to Feb 13	Nov 18 to Dec 23
Number of epidemic days		57	68	37	106	35	36
Absenteeism	Number of enrolled children	25,800	26,306	25,983	25,734	25,218	24,368
	Total number of absentees	41,835	52,004	34,622	55,309	42,299	28,187
	Mean rate of absentees (Note 2)	3.4	3.4	4.7	2.8	6.7	3.3
	Highest rate of absentees	6.2	9.4	10.5	4.7	15.0	5.6
Estimated total number of absentee cases (Note 3)		18,100	24,400	16,200	(Note 4) 24,200 (13,500)	21,400	11,700

(Note 1) The criterion of an absentee rate of 2% or more was used to determine the period.
(Note 2) The rate was calculated by adding the estimated total number of absentees per class during class closure (25) to the total number of absentees.
(Note 3) The value was calculated by the following formula:

$$\frac{\text{(Total number of absentees + Number of closed classes} \times 25)}{\text{(Mean number of days absent per each absentee case: 2.5 days)}}$$

(Note 4) The number in parentheses is a corrected value. See the text.

Table 7. Number of Closed Classes, Grades, and Schools during Influenza Epidemic Periods by School Year (Elementary Schools in Maebashi City).

School year	1980	1981	1982	1983	1984	1985
Number of schools	36	37	38	39	39	39
Number of schools with class and grade closure (%)	27 (75.0)	35 (94.6)	24 (63.2)	23 (59.0)	34 (87.2)	19 (48.7)
Number of classes	685	689	689	684	671	645
Number of closed classes (%)	134 (19.6)	363 (52.7)	237 (34.4)	206 (30.1)	451 (67.2)	42 (6.5)
Number of closed grades	10	13	13	0	15	2
Number of closed schools	1	0	0	1	1	0

(iii) Numerical comparison of epidemics

Table 6 compares the epidemics of different fiscal years with respect to a few numerical measures, including the number of epidemic days and absentees. Two epidemics in fiscal 1981 (Type B and A/H_3N_2) occurred consecutively and partly overlapped, and thus the two epidemics are combined into one for presentation purposes.

The epidemic period and the number of days were determined according to the criterion of an absentee rate of 2% or more as described previously. The total number of absentees does not include those who were absent because of class closures.

As described in the preceding paragraph, the mean rate of absentees was calculated by dividing the numerator (the estimated total number of absentees per class closure [25] multiplied by the number of closed classes was added to the total number of absentees) by the denominator (the total number of enrolled children multiplied by the number of school days) and shown in percentages.

The number of closed classes used in the calculation was based on the class closure survey conducted by the municipal board of education. The number of closed classes and the number of closed schools are shown in Table 7.

The highest rate of absenteeism was calculated by dividing the number of absentees on the day by the denominator (the total number of enrolled children minus the number of children absent because of class closure). The estimated total number of absentee cases was calculated by the following formula:

$$\frac{\text{Total number of absentees} + \text{Number of closed classes} \times 25}{\text{Mean number of days absent per each absentee case: 2.5 days}}$$

The value of 2.5 days used in the denominator of the formula was calculated from the individual absentee survey conducted at designated schools. The number of absentee cases in this context is not related to the number of days absent. A series of absentees for 1 day or more during the epidemic period was considered a single case, and the number of cases was determined. If a single child was absent twice or more, the number of all cases was counted. Needless to say, not all absentees were attributed to influenza.

However, values related to the A/H_1N_1 epidemic in fiscal 1983 require correction. As described above, the influenza epidemic appeared to end by mid February at the latest. If so, the estimated total number of absentee cases would decrease by approximately 16%. Furthermore, the results of HI antibody titer testing at the designated schools suggest that infected persons accounted for approximately 60% of absentees during an epidemic with the highest rate of absenteeism exceeding 5%. However, the proportion appeared to be about 40% during the epidemic. If a correction is made to adjust the proportion to about 60%, the estimated total number of absentee cases is 13,500 persons, which is in good agreement with our clinical impression. The value is provided in parenthesis in the table.

Thus, an attempt was made to numerically evaluate epidemic curves constructed on the basis of absenteeism rates as shown previously. This approach facilitates the comparison of parameters between Maebashi City and the country, prefectures, or other areas.

Table 8. Report on Influenza-like Illness Surveillance Program by the Gunma Medical Association (data on Maebashi City).

Survey period	Nov 1980 to Mar 1981	Jan 1982 to Mar 1982	Dec 1982 to Mar 1983	Dec 1983 to Feb 1984	Dec 1984 to Feb 1985	Dec 1985 to Feb 1986
Total number of reported patients	4,967	12,765	16,528	3,878	16,587	12,297
Number of elementary schoolchildren reported (%)	1,128 (25.1)	3,259 (25.5)	4,178 (25.3)	1,007 (26.0)	5,407 (32.6)	2,613 (21.3)

3) Comparison of influenza epidemic information between the Gunma Medical Association and the Ministry of Health and Welfare

For comparison, data on Maebashi City were excerpted from the Report on the Notification of Patients with Influenza (Including Influenza-like Illness) by the Gunma Medical Association (the Gunma Medical Association started the Report on the Notification of Patients with Epidemic Diseases in fiscal 1976 and changed its name to the one described above when the Ministry of

Health and Welfare started the National Epidemiological Surveillance of Infectious Diseases).

Table 8 shows again the total number of reported patients by fiscal year and the number and percentage of elementary schoolchildren relative to the total number of those patients. Age groups in the report include preschool children, elementary schoolchildren, junior high school students, and high school students or older, and the proportion of age groups for each fiscal year is shown in Figure 3. In each year, the proportion of high school students or older was highest, followed by elementary schoolchildren, junior high school students, and preschool children. There was no substantial difference in the pattern across the epidemic periods. In fiscal 1980 and 1981, data from December to March in the following year were reported. From fiscal 1982 onward, reporting was started in December and terminated in February of the following year. Table 8 shows the total of monthly data.

An unexpectedly small number of patients reported from November 1980 to March 1981 was probably the result of the influence of the following conditions: As described in the initial part of this section, the Gunma Medical Association temporarily stopped the program when the Ministry of Health and Welfare started the National Epidemiological Surveillance of Infectious Diseases and soon resumed the program. The number of patients was also small the following year probably because the A/H_3N_2 epidemic in March was not identified as an influenza epidemic by many clinics. During the A/H_1N_1 epidemic from December 1983 to February 1984, the number of reported patients was very small, suggesting that the corrective value of the estimated total number of absentee cases may better reflect the actual situation.

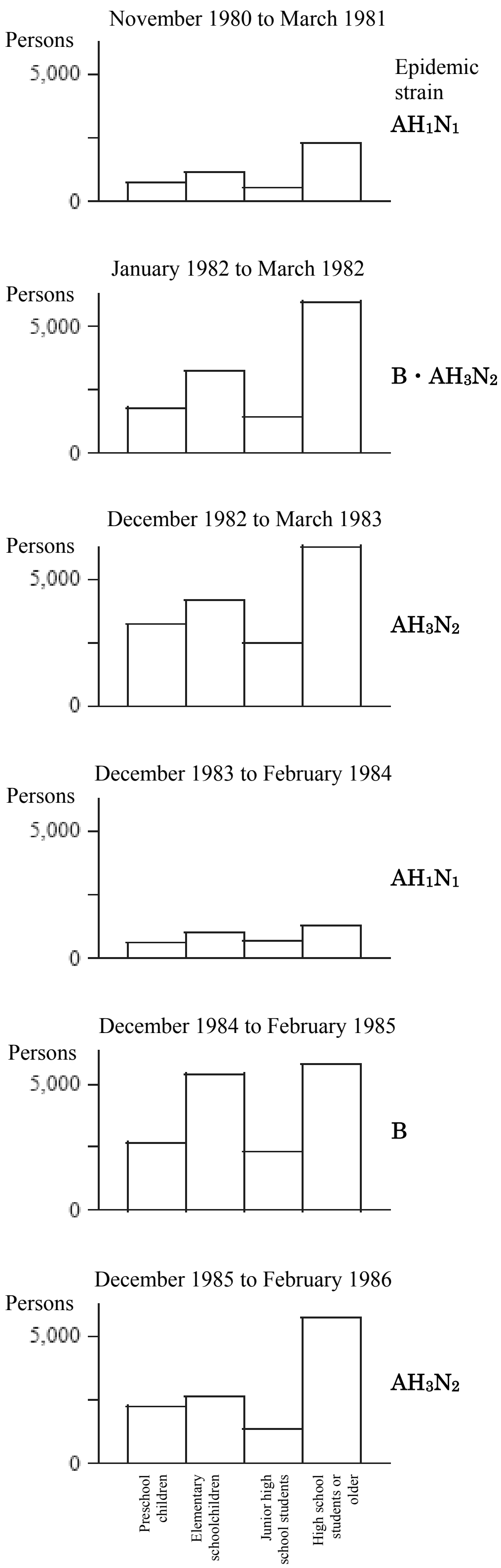


Figure 3. Age Group-Specific Incidence by Fiscal Year in the Report on Patients with Influenza-like Illness in Maebashi City.

The proportion of elementary schoolchildren in the total number of reported patients was constant at about 25% from fiscal 1980 to 1984 but exceeded 30% during the influenza B epidemic in 1985. This should reflect an explosive epidemic situation during the period. In contrast, the low proportion of 20% the following year appeared to reflect the fact that school winter holidays started during the decline phase of the epidemic.

With respect to the number of reported patients in this survey, the diagnostic criteria may differ slightly among the reporting medical institutions because it is difficult to distinguish influenza from the common cold. However, this is a good measure of epidemics in the city because all members of the Maebashi Medical Association participated in the survey, because the members did not change substantially, because the reporting was performed over time under specific conditions, and because the proportion of patients with influenza visiting national or public hospitals in the city, which did not participate in the survey, was not large. These analyses suggest that epidemics in elementary schools closely paralleled epidemics in the city and well reflected the scale of epidemics in the city.

Next, a comparison was made with the number of cases of influenza-like illness in Japan documented in the Epidemic Control Information by the Ministry of Health and Welfare. Data for fiscal 1980 to 1985 are shown in Table 9. The figures were calculated on the assumption that persons on sick leave and those with fever on the day before class closures at high schools, junior high schools, elementary schools, and some kindergartens across Japan had influenza-like illness. The total of persons reported weekly from the prefectures was published as the number of patients during the epidemic period. This represented the size of the epidemic in the Japanese school population, and the Ministry of Health and Welfare also used this as a relative measure of the size of the epidemic in Japan.

When this was compared with the estimated total number of absentee cases in Maebashi City with the value in fiscal 1980 being considered 1.0, the epidemic sizes in fiscal 1981, 1984, and 1985 were about twice as large in Japan as in Maebashi City. However, the fluctuation pattern was similar in the two populations.

Next, a similar comparison was made with curves showing the number of cases of influenza-like illness in Japan compiled by the Ministry of Health and Welfare. Because data in the weekly reports described above were plotted on a semilogarithmic plot, the epidemic curves in Maebashi City were converted to semilogarithmic plots for comparison. Figure 4 shows striking similarities in the epidemic period, epidemic duration, relative epidemic size, and epidemic pattern for each fiscal year.

Taken together, influenza epidemics in elementary schools in Maebashi City paralleled school epidemics nationwide. Overall, Japan is a school-based, mass influenza vaccination area, although the overall vaccination rate is not high. It is safe to say that Maebashi City, a non-vaccinated area, does not have a special epidemic situation compared with Japan as a whole.

Table 9. Number of Patients with Influenza-like Illness in Japan Compiled by the Ministry of Health and Welfare.

Epidemic period	1980–81	1981–82	1982–83	1983–84	1984–85	1985–86
Total number of patients	555,399	1,690,628	500,506	433,754	1,050,607	640,846

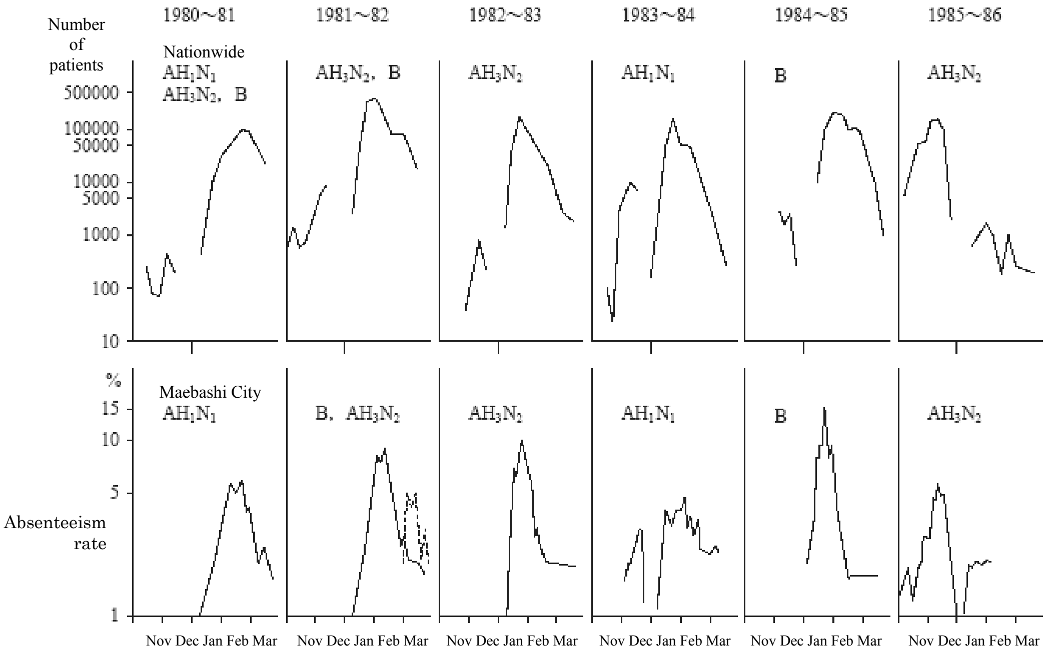


Figure 4. Comparison of the Curve Showing the Weekly Number of Patients with Influenza-like Illness across Japan and the Curve Showing the Absentee Rate at all Elementary Schools in Maebashi City for Each Fiscal Year.

B. Comparison of epidemics between non-vaccinated areas and vaccinated areas in the prefecture

In the previous chapter, we reviewed epidemics in Maebashi City, a non-vaccinated area, and found no evidence that epidemics in Maebashi City had features peculiar to a non-vaccinated area.

Our next concern was whether the size of the epidemic was greater in Maebashi City, a non-vaccinated area, than in the surrounding, vaccinated areas in the prefecture. The appropriateness of our judgment depends on the issues. However, there is no official information system that can be used to compare the epidemics between Maebashi City and a comparable area. When examining well-planned studies of the preventive effect of vaccines on local epidemics, we have to rely on the literature from foreign countries. No reports are available that demonstrate the efficacy of the mass vaccination of schoolchildren in suppressing local epidemics and can be used as a reference control. Thus, we analyzed preexisting data and those collected by all possible means to elucidate the relative size of the epidemic in Maebashi City, a non-vaccinated area.

1) Incidence of influenza-like illness by area

On the basis of the Influenza-like Illness Surveillance Report by the Gunma Medical Association, we selected medical associations in Maebashi City, Takasaki City, Kiryu City, Isesaki City/Sawa-gun, and Ota City (a plain, southern part of the prefecture), Numata City/Tone-gun (a northern intermountain area of the prefecture), and Annaka City/Usui-gun (non-vaccinated area located to the West of Takasaki City) and presented the number of reported patients per 100,000 population in each area to which each medical association belonged for comparison. Figure 5 shows the number of patients in non-vaccinated areas of Maebashi City and Annaka City/Usui-gun (on the left) and in the vaccinated areas of five gun/cities (on the right) from fiscal 1982 to 1985. The major epidemic strains are shown on the left of each figure. Overall, each figure shows the epidemic scale in each year, and there are naturally some regional differences. However, it is difficult to identify a certain difference between non-vaccinated areas and vaccinated areas.

Not all reported patients had influenza. However, given the difficulty in the clinical diagnosis of influenza, it may be meaningless to pursue too strict criteria. The number of patients reported by physicians is a measure that is considered reliable internationally. Thus, the figure indicates that the mass vaccination of schoolchildren does not have a substantial effect on the number of patients in these areas.

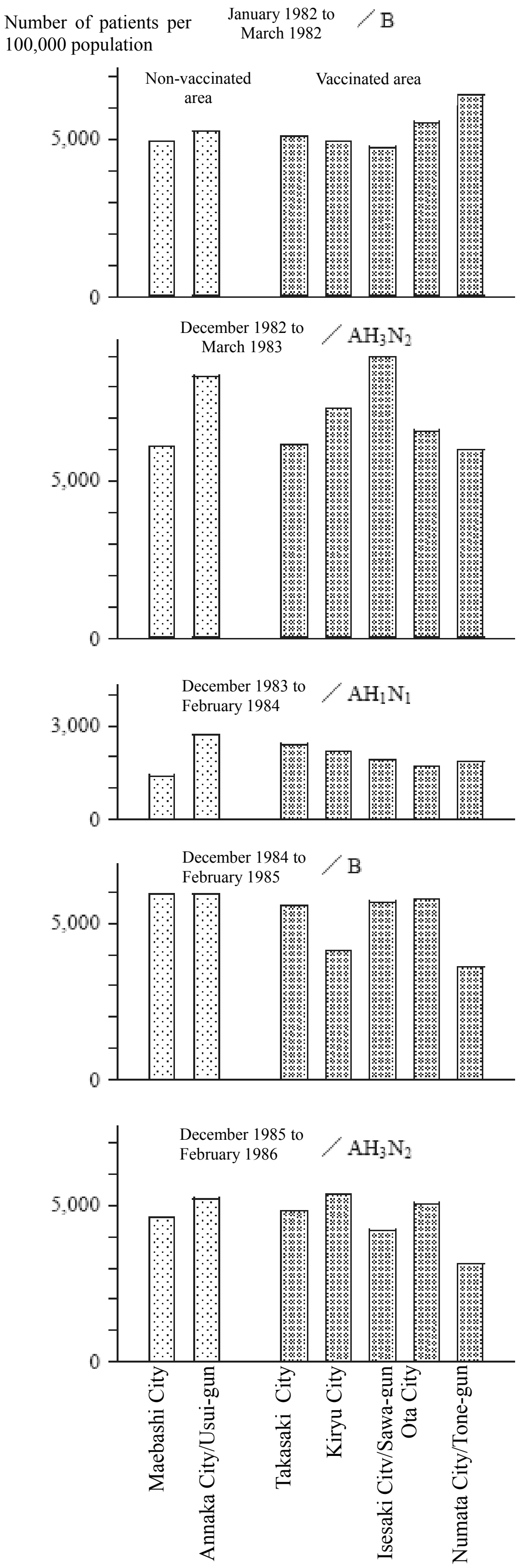


Figure 5. Incidence of Influenza-like Illness in Each Area of Gunma Prefecture.

2) Influenza epidemics evaluated from National Health Insurance medical fees

We investigated the effect of influenza epidemics on health care costs and the impact of influenza vaccinations on the costs by using the statistics of National Health Insurance medical fees, which was relatively easily available.

As described in the Remarks column of Table 10, the number of clinical visits, total medical fee points, and medical fee points per visit were compared between the usual pre-influenza epidemic period (September to November) and the influenza epidemic period (December to February); comparison was made separately in non-vaccinated areas (Maebashi City and Annaka City combined) and vaccinated areas (Takasaki City, Kiryu City, Isesaki City, and Ota City combined). In fiscal 1985, however, a comparison was made between the August-to-October period and the November-to-January period because the epidemic peaked in December. For comparison, the ratio before and after the epidemic as described above was determined because amendments were made to insurance systems, including the health insurance law for the elderly during the survey period.

Figure 6 illustrates the ratios. A ratio of 1.0 indicates no change in the number of visits or medical fee point between the pre-epidemic period and the epidemic period. Ratios greater than 1.0 indicate an increase, and ratios less than 1.0 indicate a decrease. As shown in the figure, there was no significant difference between non-vaccimated area and vaccinated area in Number of visits. The ratios of the total medical fee points and medical fee points per visit were evidently higher in non-vaccinated areas in fiscal 1985. However, this was because the total medical fee points and medical fee points per visit in the pre-influenza epidemic period were considerably lower than those in the previous fiscal year or two in non-vaccimated area. These results demonstrate that mass influenza vaccination of schoolchildren does not have a substantial effect on health care costs.

Table 10. Comparison of the National Health Insurance-Covered Medical Care Before and After the Epidemic Period in Influenza-Vaccinated and Non-Vaccinated Areas.*

Fiscal year	Item	Non-vaccinated areas (Maebashi and Annaka)			Vaccinated areas (Takasaki, Kiryu, Isesaki, and Ota Cities)			Remarks
		Before epidemic	Epidemic period	Epidemic period / Before epidemic	Before epidemic	Epidemic period	Epidemic period / Before epidemic	
1982	Number of visits	157,840	151,537	0.960	298,471	287,684	0.964	Survey period Before: Sep to Nov
	Medical fee point	× 1000 275,459	× 1000 247,316	0.898	× 1000 538,296	× 1000 485,477	0.902	
	Medical fee point per visit	1,745	1,634	0.936	1,804	1,688	0.936	Epidemic: Dec to Feb
1983	Number of visits	115,828	117,089	1.011	222,959	224,356	1.006	Survey period Before: Sep to Nov
	Medical fee point	× 1000 173,803	× 1000 176,376	1.015	× 1000 340,917	× 1000 338,411	0.993	
	Medical fee point per visit	1,501	1,506	1.003	1,529	1,508	0.986	Epidemic: Dec to Feb
1984	Number of visits	110,449	112,307	1.017	210,534	212,589	1.010	Survey period Before: Sep to Nov
	Medical fee point	× 1000 171,544	× 1000 167,261	0.975	× 1000 315,705	× 1000 308,863	0.978	
	Medical fee point per visit	1,553	1,489	0.959	1,500	1,453	0.969	Epidemic: Dec to Feb
1985	Number of visits	105,285	108,302	1.029	198,482	208,163	1.049	Survey period Before: Aug to Oct
	Medical fee point	× 1000 151,181	× 1000 173,812	1.150	× 1000 321,920	× 1000 329,317	1.023	
	Medical fee point per visit	1,436	1,605	1.118	1,622	1,582	0.975	Epidemic: Nov to Jan

* The National Health Insurance does not include the health insurance for elderly and for retired persons. The large difference between fiscal 1982 and fiscal 1983 is attributed to the implementation of the health insurance law for the elderly.

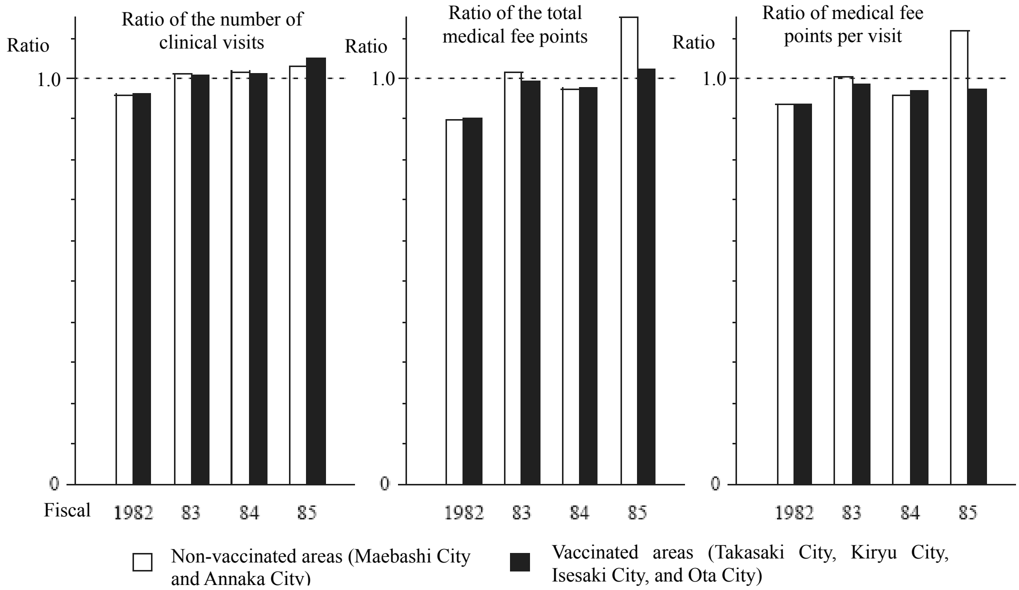


Figure 6. Comparison of the Ratio of National Health Insurance-Covered Medical Care During the Epidemic Period Relative to That Before the Epidemic Period Between Influenza-vaccinated and Non-vaccinated Areas.

However, we found two unexpected results. First, an influenza epidemic period is the busiest time of year for physicians, particularly those at pediatric clinics. According to the statistics, the ratio of the number of visits, for example, marginally exceeded 1.0. This indicates that the number was insignificant when compared with the total number of visits.

Second, ratios in fiscal 1982 (before the enactment of the health insurance law for the elderly) were smaller than in fiscal 1983 and later. After implementation of the health insurance law for the elderly, the number of visits by eligible persons decreased by approximately 30%. This indicated that the number of visits made by persons eligible for the National Health Insurance increased by approximately 2% on average during epidemic periods and that the number of visits by persons eligible for the health insurance for the elderly (persons 70 years of age or older) decreased by approximately 2%. Older individuals appeared to visit clinics less frequently during influenza epidemic periods. The survey involving older individuals was conducted for a single fiscal year, and a definite conclusion must await further investigation. At any rate, discontinuation of influenza vaccination is unlikely to increase health care costs.

Japanese insurance systems include the government-managed social insurance, mutual aid associations, and company-sponsored health insurance societies. These systems differ to some extent with respect to age, physical, social, and financial conditions of insured family members. The influence of influenza epidemics on these systems is an interesting issue but beyond our control.

3) Comparison on the basis of mortality curves

Influenza epidemics are known to be associated with an increased mortality from chronic respiratory disease, heart disease, rheumatism, diabetes mellitus, or tumors. Common direct causes include pneumonia and heart failure, which are infrequent in preschool children but very frequent in older individuals. These deaths, in the form of excess mortality, are used as a measure of epidemics. Monthly mortality rates during a period without influenza epidemics are used to calculate the expected value of the mortality rate of pneumonia and influenza in each month of year. When the expected mortality curve drawn on the basis of the values is superimposed on the actual mortality curve, the portion exceeding the expected mortality curve visually represents the excess mortality rate.

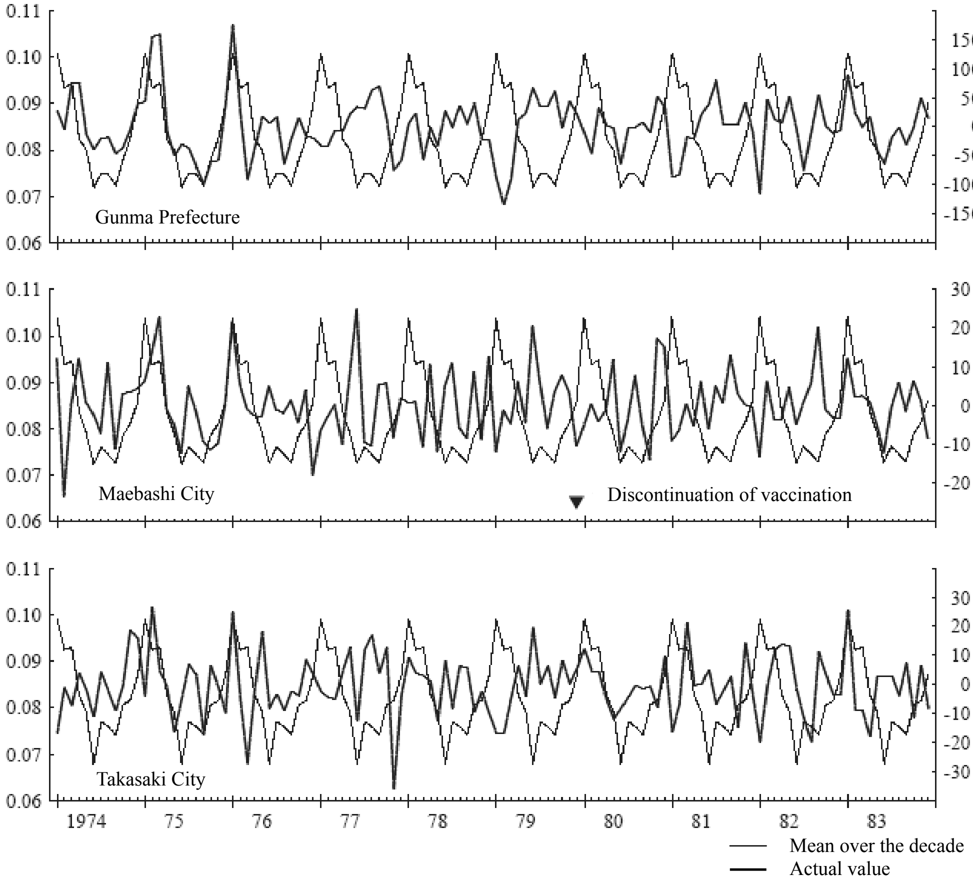


Figure 7. Statistics of Excess Mortality.

However, we did not have sufficient statistical mortality data for calculation of the expected mortality rate and thus examined the change in mortality rate before and after discontinuation of vaccination while using the mean monthly mortality rate over the previous 10 years as a reference.

Figure 7 shows the monthly mortality curves in Gunma Prefecture, Maebashi City, and Takasaki City. As described previously, Takasaki City is a neighboring city with an annual vaccination rate exceeding 80%. The thin line consisting of annual repeats of the same waveform is the mean mortality curve. There is no substantial difference in the waveform in any of the figures. Actual mortality curves, shown as a thick line, provide no evidence that the actual mortality rate after discontinuation of vaccinations in Maebashi City considerably exceeded the mean mortality rate during influenza epidemic periods. The indirect analysis suggests that discontinuation of mass vaccinations of schoolchildren is unlikely to cause excess mortality.

C. Vaccine efficacy in terms of the absenteeism rate in elementary schools

As described in the previous chapter, mass influenza vaccinations of schoolchildren do not substantially reduce local epidemics. What benefit do schoolchildren (vaccinees) receive from vaccinations?

The effect of vaccines on the absenteeism rate was evaluated by collecting data on municipal elementary schools from the survey report on the number of absentees for all high schools, junior high schools, and elementary schools in the prefecture during epidemic periods from fiscal 1984 to 1985, which was compiled jointly by the prefectural board of education and the institute for public health. It should be noted that the effect of vaccines in this context was related to the protection at the level of population, not at the level of individuals.

1) Survey methods

A survey form was distributed to schools via municipal boards of education, and a survey was conducted in each class. Survey items included (1) the absence or early leave because of the common cold, (2) body temperature of 37°C or higher, (3) influenza vaccination status, (4) the presence or absence of class closures and duration, and (5) the presence or absence of shorter school hours. Data on (1), (2), and (3) are used in this section.

The survey was conducted on school days from January 8 to February 28, 1985 (fiscal 1984) and from November 3 to December 28, 1985 (fiscal 1985). At each school, an influenza epidemic period was determined, a period during which the absentee rate from influenza-like illness was 2% or more. The daily rate of absentees was expressed as a percentage of the daily number of absentees to the number of enrolled children. During class closures, it was calculated on the assumption that 20% of enrolled children were absent. In this context, influenza absentees (hereafter simply referred to as patients) were those who were absent during epidemic periods determined at each school and met the following criteria.

(1) Those who had a temperature of 37°C or more and were absent for at least 2 consecutive days.

(2) Those who had an unknown temperature and were absent for at least 3 consecutive days.

According to the number of doses of the influenza vaccine, these patients were classified into three groups of the non-vaccinated group, the one-dose group, and the two-dose group and summarized. The absentee rate in each group was considered the incidence.

2) Selection of control areas

The primary objective here was to make a comparison between non-vaccinated areas and vaccinated areas, and thus 5 of 11 cities in the prefecture were selected for the comparison. Maebashi City and Annaka City were selected as non-vaccinated areas, and Takasaki City, Kiryu City, and Isesaki City were selected as vaccinated areas.

The three cities were selected as vaccinated areas because of understandability and other relevant reasons. Takasaki City is the second-most populated city next to Maebashi City in the prefecture and similar to Maebashi City in scale and geographical conditions. It is located to the west of Maebashi City. It is a transportation hub in the prefecture and a high-traffic area. It had been enthusiastic for influenza vaccinations with a vaccination rate of 80% or more. In this respect, it contrasted markedly with Maebashi City.

Located to the west of Takasaki City, Annaka City is a small city with a population less than 50,000 and lies along the Usui River.

Among the three cities, Takasaki City is most populated, followed by Kiryu City and Isesaki City. Isesaki City is located to the southeast of Maebashi City, and many people commute between Isesaki City and Maebashi City. Isesaki City is bounded by Saitama Prefecture to the south, and many people shuttle between the city and Tokyo via the Tobu line or the Takasaki line by way of Honjo City. Consequently, an influenza epidemic always starts early.

Kiryu City is adjacent to Tochigi Prefecture and located to the east of Maebashi City; there are three municipalities between Kiryu and Maebashi. Kiryu City was chosen to represent epidemics in the southeast area of the plain field in the prefecture. Vaccination rates in Kiryu City and Isesaki City were similar, 59% and 59% in fiscal 1984, and 47.7% and 51.0%, respectively, in fiscal 1985, indicating a decrease of about 10 percentage points. In the same period, there was a decrease from 85.6% to 80.5% (approximately 5 percentage points) in Takasaki City.

According to the distribution of total absentee rates, epidemic conditions at municipal elementary schools in the prefecture were classified into two groups in fiscal 1984: a group with a rate of 40% to 50% and a group with a rate of about 25%. The three cities belonged to the former group. In fiscal 1985, there was no substantial difference in the total absentee rate among the three cities. When the size of the epidemic, which was estimated from the epidemic period and the highest rate of absenteeism, was classified into three groups (large, middle, small), the three cities belonged to the large group. Thus, it was deemed reasonable to select these three cities as controls.

The addition of the results from the remaining 6 cities of the 11 cities in the prefecture did not change overall figures that necessitated modification of our conclusions. The addition of intermountain cities with a population of 40,000 to 50,000 and different geographic environments appeared to make the comparison difficult in many cases.

3) Incidence of influenza in elementary schoolchildren

Tables 11 and 12 show the incidence of influenza among elementary schoolchildren in the five cities described in the preceding section. Maebashi City and Annaka City are areas without influenza vaccinations, whereas Takasaki City, Kiryu City, and Isesaki City listed below are vaccinated areas. Study subjects accounted for at least 99% of enrolled children in each city. The subjects are divided into three groups according to vaccination status, and the number of patients and the incidence (%) are presented for each group. Table 11 shows the influenza B epidemic in fiscal 1984, and Table 12 shows the A/H_3N_2 epidemic in fiscal 1985.

Overall, the incidence was above 40% in fiscal 1984 and above 20% in fiscal 1985, indicating that the epidemic in fiscal 1984 was larger. At maximum, the incidence differed by 11.8 percentage points in fiscal 1984 and 8.1 percentage points in fiscal 1985. These differences, probably reflecting regional differences in epidemics, were not substantial. When the incidence was compared separately in non-vaccinated areas and vaccinated areas, there were no substantial differences between the fiscal years.

Table 11. Incidence of Influenza in Elementary Schoolchildren in Fiscal 1984.

City		Total number of subjects	Non-vaccinated group	One-dose group	Two-dose group
Maebashi City	Number of subjects (%)	25,122	25,101 (99.9)	18 (0.1)	3
	Number of patients	10,743	10,738	5	0
	Incidence (%)	42.8	42.8	27.8	0
Annaka City	Number of subjects (%)	4,021	4,021 (100)	0 (0)	0 (0)
	Number of patients	1,832	1,832	0	0
	Incidence (%)	45.6	45.6		
Takasaki City	Number of subjects (%)	22,119	1,887 (8.5)	1,291 (5.8)	18,941 (85.6)
	Number of patients	8,865	1,017	592	7,254
	Incidence (%)	40.1	53.9	45.9	38.3
Kiryu City	Number of subjects (%)	12,374	2,751 (22.2)	2,318 (18.7)	7,305 (59.0)
	Number of patients	5,324	1,425	1,039	2,860
	Incidence (%)	43.0	51.8	44.8	39.2
Isesaki City	Number of subjects (%)	10,834	2,603 (24.0)	1,836 (16.9)	6,395 (59.0)
	Number of patients	5,628	1,520	967	3,141
	Incidence (%)	51.9	58.4	52.7	49.1

* The collection rate was 99.0% or more.

Table 12. Incidence of Influenza in Elementary Schoolchildren in Fiscal 1985.

City		Total number of subjects	Non-vaccinated group	One-dose group	Two-dose group
Maebashi City	Number of subjects (%)	24,266	24,249 (99.0)	10 (0.0)	7 (0.0)
	Number of patients	6,714	6,709	5	0
	Incidence (%)	27.7	27.7	50.0	0
Annaka City	Number of subjects (%)	4,071	4,056 (99.6)	11 (0.3)	4 (0.1)
	Number of patients	903	899	3	1
	Incidence (%)	22.2	22.2	27.3	25.0
Takasaki City	Number of subjects (%)	21,381	2,063 (9.6)	2,106 (9.8)	17,212 (80.5)
	Number of patients	4,481	637	640	3,204
	Incidence (%)	21.0	30.9	30.4	18.6
Kiryu City	Number of subjects (%)	11,657	2,628 (22.5)	3,470 (29.8)	5,559 (47.7)
	Number of patients	2,933	846	817	1,270
	Incidence (%)	25.2	32.2	23.5	22.8
Isesaki City	Number of subjects (%)	10,649	3,011 (28.3)	2,202 (20.7)	5,436 (51.0)
	Number of patients	3,099	1,081	763	1,255
	Incidence (%)	29.1	35.9	34.7	23.1

In vaccinated areas, however, the incidence decreased in the following order: the non-vaccinated group, the one-dose group, and the two-dose group. The vaccine efficacy rate calculated by a conventional method with the non-vaccinated group as a control was 29%, 24%, and 16% in Takasaki City, Kiryu City, and Isesaki City, respectively, in fiscal 1984 and 40%, 29%, and 36% in fiscal 1985. Indeed, Takasaki City with a vaccination rate of 80% or more had a high efficacy rate. In Kiryu City and Isesaki City with a low vaccination rate (60% or less), however, there was no clear relationship between the vaccination rate and epidemic size. Still, these values were much lower than nominal vaccine efficacy rates (70% or more). Moreover, it is questionable whether these low efficacy rates really represent vaccine efficacy rates.

4) Investigation of the vaccine efficacy rate

To identify problems, the non-vaccinated area (Maebashi City) was compared with the vaccinated area (Takasaki City, Kiryu City, and Isesaki City combined) as shown in Figure 8. The overall incidence in the three cities (43.7% in fiscal 1984 and 24.1% in fiscal 1985) was similar to that in Maebashi City. When the non-vaccinated group in the three cities was used as a control, the vaccine efficacy rate was 25.8% in fiscal 1984 and 39.0% in fiscal 1985.

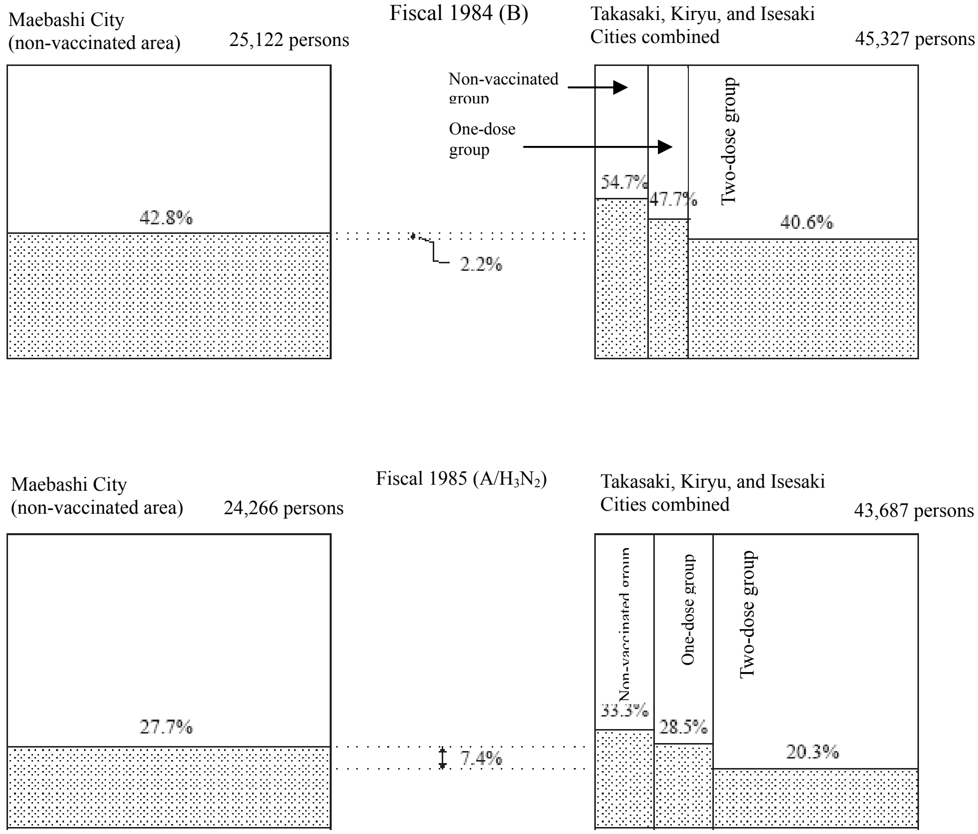


Figure 8. Incidence of Influenza in Elementary Schoolchildren by Vaccination Status.

Here, a problem looms. The problem is whether the non-vaccinated group meets the conditions for a control group. On the day of mass vaccinations, weak children susceptible to the common cold must be considered to have a contraindication to the vaccination and receive no dose. Children with asthma, who account for about 5% of children in common elementary schools, are most likely to be considered to have a contraindication. In fiscal 1985 when vaccinations were given during the epidemic period, children with fever or other physical abnormalities on the day were likely to be considered to have a contraindication to the vaccination. Many of the children possibly had influenza. The non-vaccinated group, including these children, should not have conditions for a randomly selected, statistically relevant, control group. In short, the group had different characteristics. This may explain the markedly higher incidence in the non-vaccinated group than that in Maebashi City.

On the assumption that the epidemic size was similar in Maebashi City and the three cities, the absolute difference in the incidence between Maebashi City and the two-dose group of the three cities was 2.2% in fiscal 1984 and 7.4% in fiscal 1985. Accordingly, the vaccine efficacy rate decreased to only 5.1% in the former case and 26.7% in the latter case. This is in consistent with the previous notion that vaccine is less effective against type B.

D. Influenza epidemics in elementary schools on the basis of HI antibody titer

The results of the observation and analysis of influenza epidemics on the basis of HI antibody titer are described below. Humoral antibodies (blood antibodies) involved in immunity against influenza are largely divided into virus-neutralizing antibodies, hemagglutination-inhibiting antibodies (HI antibodies), anti-neuraminidase antibodies, and other several types of antibodies detected by complement-fixation (CF) reaction. In addition, IgA antibodies are secreted from the surface of the respiratory mucosa. Among these blood antibodies, HI antibodies are well known to be effective in preventing infection. Antibody titers expressed as the dilution ratio of serum are extensively used as a measure of the degree of immunity against influenza and a method for serodiagnosis of influenza in clinical settings. Testing techniques are relatively easy, and methods for testing many samples in a relatively short time have been developed.

Therefore, we tried to utilize the HI antibody titer to monitor epidemics. Although easy methods were available, it was impossible to measure HI antibody titers in all schoolchildren in the city. Thus, measurements were made according to II-2 "Subjects and methods." We stress again that we followed up the same population of approximately 600 second-grade elementary schoolchildren over a period of five years until they became sixth graders. To our knowledge, there has been no such report in Japan. Although many issues remain to be examined, we used the currently available investigation results to shed light on some of problems discussed above, identify problems to be elucidated, and provide control or reference data for use in similar surveys possibly conducted in the future. This chapter also focuses on herd immunity and describes the results of our utmost efforts to solve the problems discussed in the previous chapters from the viewpoint of immunology or seroepidemiology.

1) Distribution of antibody titers by type, blood sampling period, and school

Table 13 shows the number of subjects by blood sampling period and school. There was no substantial change in the number of subjects at the five elementary schools during blood sampling periods, except for Ootone Elementary School in which the number of subjects increased by approximately 40 persons because of modification of the school district in fiscal 1984.

The total number of subjects in each period was approximately 600 persons on average. In terms of the total number of subjects, 95.4% of scheduled subjects underwent blood sampling. The majority of subjects not undergoing blood sampling took sick leave or declined to undergo blood sampling.

For the measurement of HI antibody titers, 5 mL of blood was collected. There were no problems after blood sampling. Blood samples were placed in an icebox immediately after collection and sent to the prefectural institute for public health. Sera were separated by a routine method and stored frozen in a freezer. Samples collected before and after an epidemic period (November and May [March in 1986]) were measured simultaneously in June of the following year (April in 1986) with the use of the same test strain. Unused sera were stored frozen again for further investigation.

Table 14 shows the virus strains used for the measurement of antibody titers. Each fiscal year indicates the school year, running from April through March of the following year. An asterisk in the table indicates the test strain used for investigation of the epidemic for the fiscal year. When the same type of virus was analyzed with two test strains, antibody titers determined with one of them were used for the investigation. The reason will be described later.

Table 13. Total Number of Subjects by Blood Sampling Period and School.

Blood sampling period	Shikishima Elementary School	Katsuyama Elementary School	Ootone Elementary School	Aramaki Elementary School	Utsuboi Elementary School	Total
Nov 1981	130	114	154	136	46	580
May 1982	127	111	152	141	47	578
Nov 1982	129	119	156	144	46	594
May 1983	137	122	156	150	48	613
Nov 1983	127	109	144	139	49	568
May 1984	131	115	187	143	49	625
Nov 1984	127	119	188	142	47	623
May 1985	132	116	186	140	50	624
Nov 1985	128	99	183	141	50	601
Mar 1986	132	97	181	138	50	598
Total	1,300	1,121	1,687	1,414	482	6,004

Table 14. List of Strains for the Measurement of HI Antibody Titers during Each Epidemic Period.

Fiscal 1981 (April 1981 to March 1982)	A/Kumamoto/37/79(H_1N_1) A/Bangkok/1/79(H_3N_2)* A/Niigata/102/81(H_3N_2) B/Singapore/222/79*
Fiscal 1982 (April 1982 to March 1983)	A/Kumamoto/37/79(H_1N_1) A/Niigata/102/81/(H_3N_2) A/Ishikawa/7/82(H_3N_2)* B/Singapore/222/79
Fiscal 1983 (April 1983 to March 1984)	A/Kumamoto/37/79(H_1N_1)* A/Ishikawa/7/82(H_3N_2) B/Singapore/222/79
Fiscal 1984 (April 1984 to March 1985)	A/Bangkok/10/83(H_1N_1) A/Philippine/2/82(H_3N_2) B/Singapore/222/79* B/USSR/100/83
Fiscal 1985 (April 1985 to March 1986)	A/Bangkok/10/83(H_1N_1) A/Philippine/2/82(H_3N_2)* B/USSR/100/83

Asterisk indicates the test strain used for analysis of the epidemic in the fiscal year.

Figures 9, 10, and 11 graphically show the distribution of antibody titers by type, blood sampling period, and school. Figure 9 shows the change in the distribution of A/H_1N_1-specific antibody titers. The epidemic occurred from January to March 1981. At all five elementary schools, the distribution curves of antibody titers in November 1983 showed a peak antibody titer of 128-fold. Overall, the curves then shifted progressively to the left, or the lower antibody titer. Another epidemic occurred from December 1983 to February 1984. This epidemic was small; the infection rate ranged from 20% to 29% at Shikishima, Katsuyama, and Ootone elementary schools and was only 4.1% (2 children) at Utsuboi Elementary School. Aramaki Elementary School showed an infection rate of 38.4%. For the first three schools, the portion of higher antibody titers (right tail) extended slightly. The curve for Utsuboi Elementary School remained unchanged. At Aramaki Elementary School, the curve for the distribution of antibody titers clearly shifted to the right. When the five schools were combined, the curves slightly shifted to the right. The impact of epidemic size on herd immunity was small.

In November 1984, the test strain was changed to A/Bangkok, which did not affect the continuity of the change in antibody titers. Overall, antibody titers gradually decreased. This was particularly evident at Utsuboi Elementary School, although the number of subjects was small. Needless to say, the booster effect of the small epidemic occurring from December 1983 to February 1984 should be taken into consideration to some extent. Taken together, the figure indicates that immunity acquired by natural infection is firmly maintained.

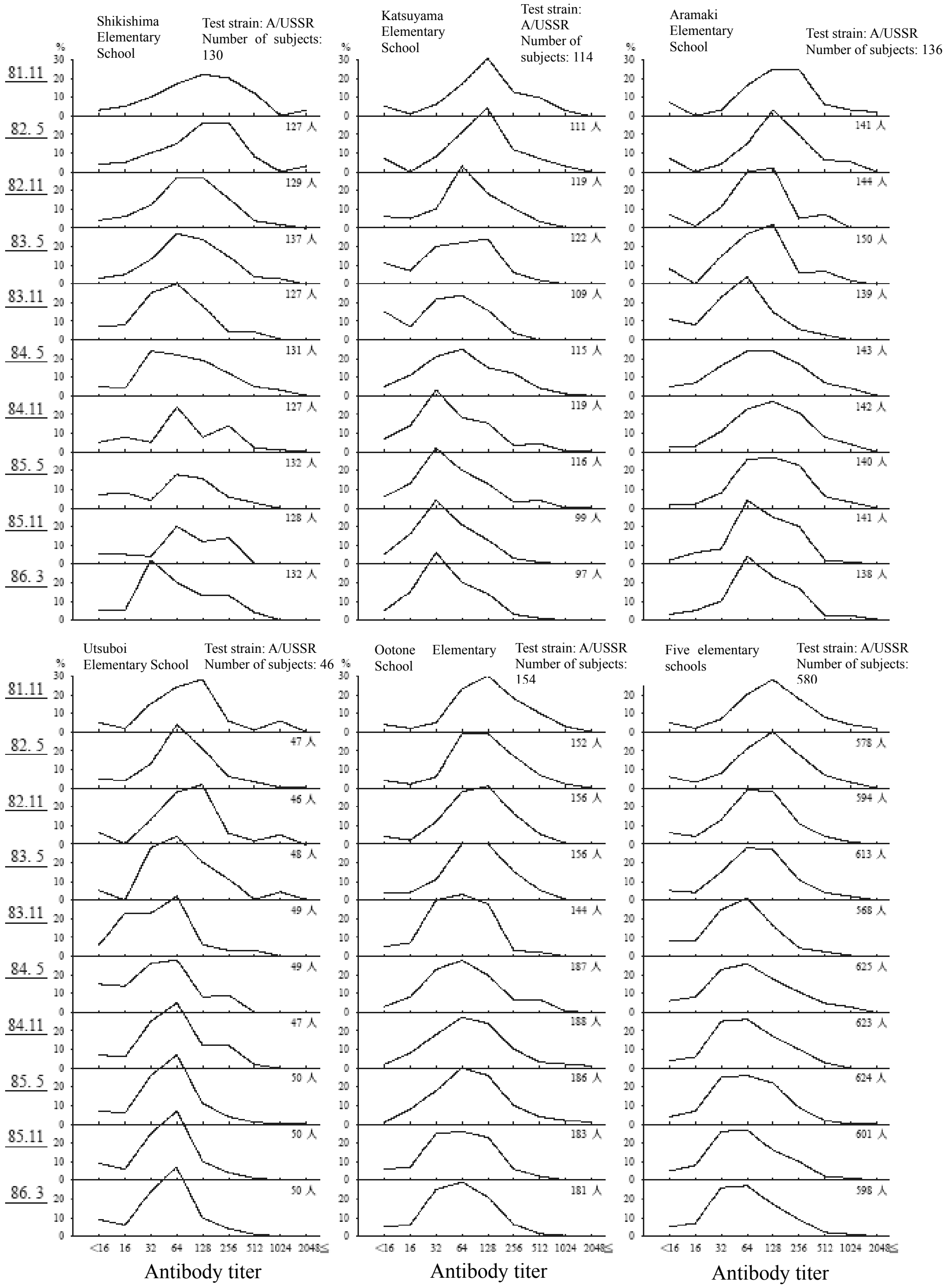


Figure 9. Distribution of Antibody Titers against A/H_1N_1 Strain by School and Blood Sampling Period.

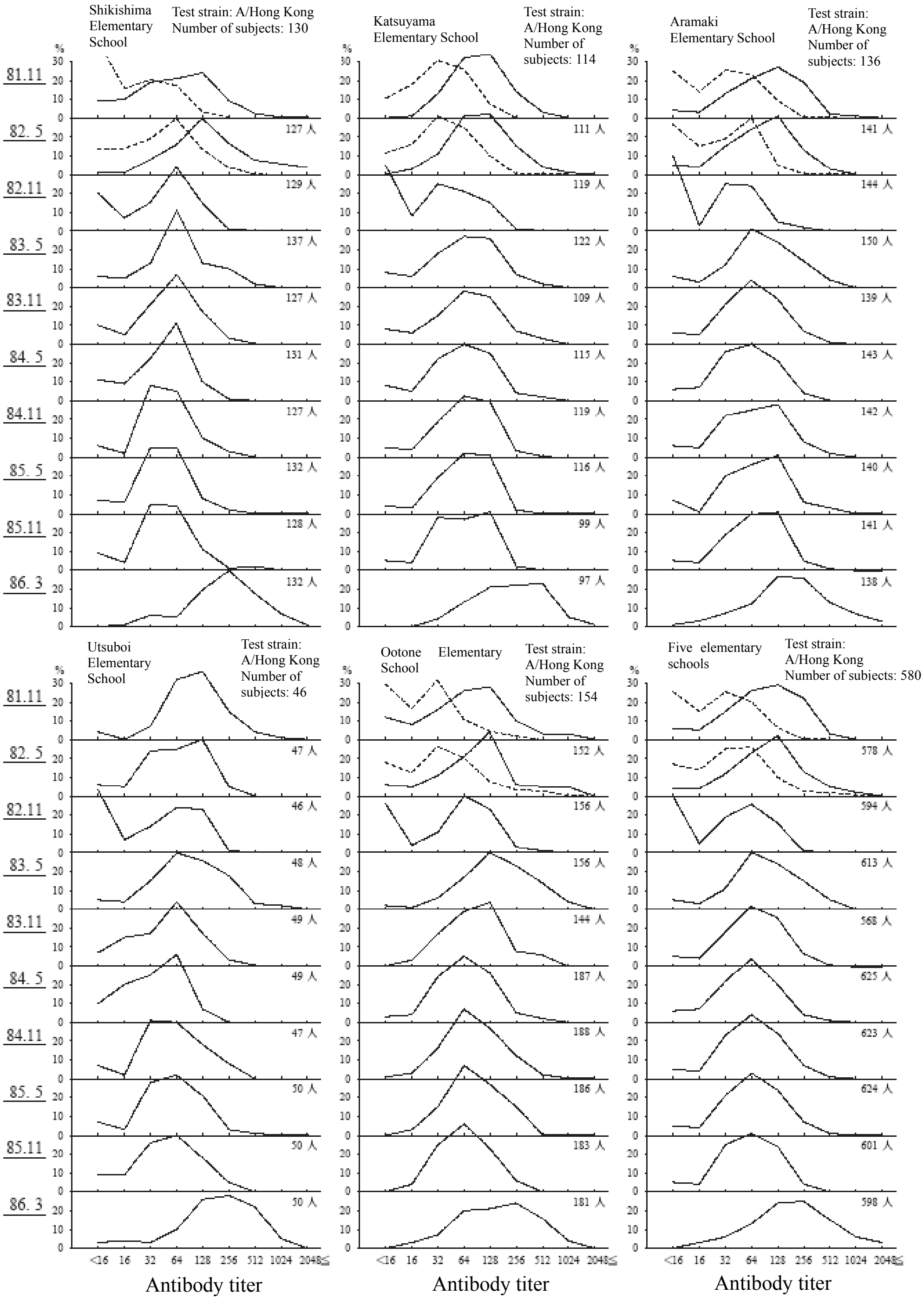


Figure 10. Distribution of Antibody Titers against A/H_3N_2 Strain by School and Blood Sampling Period.

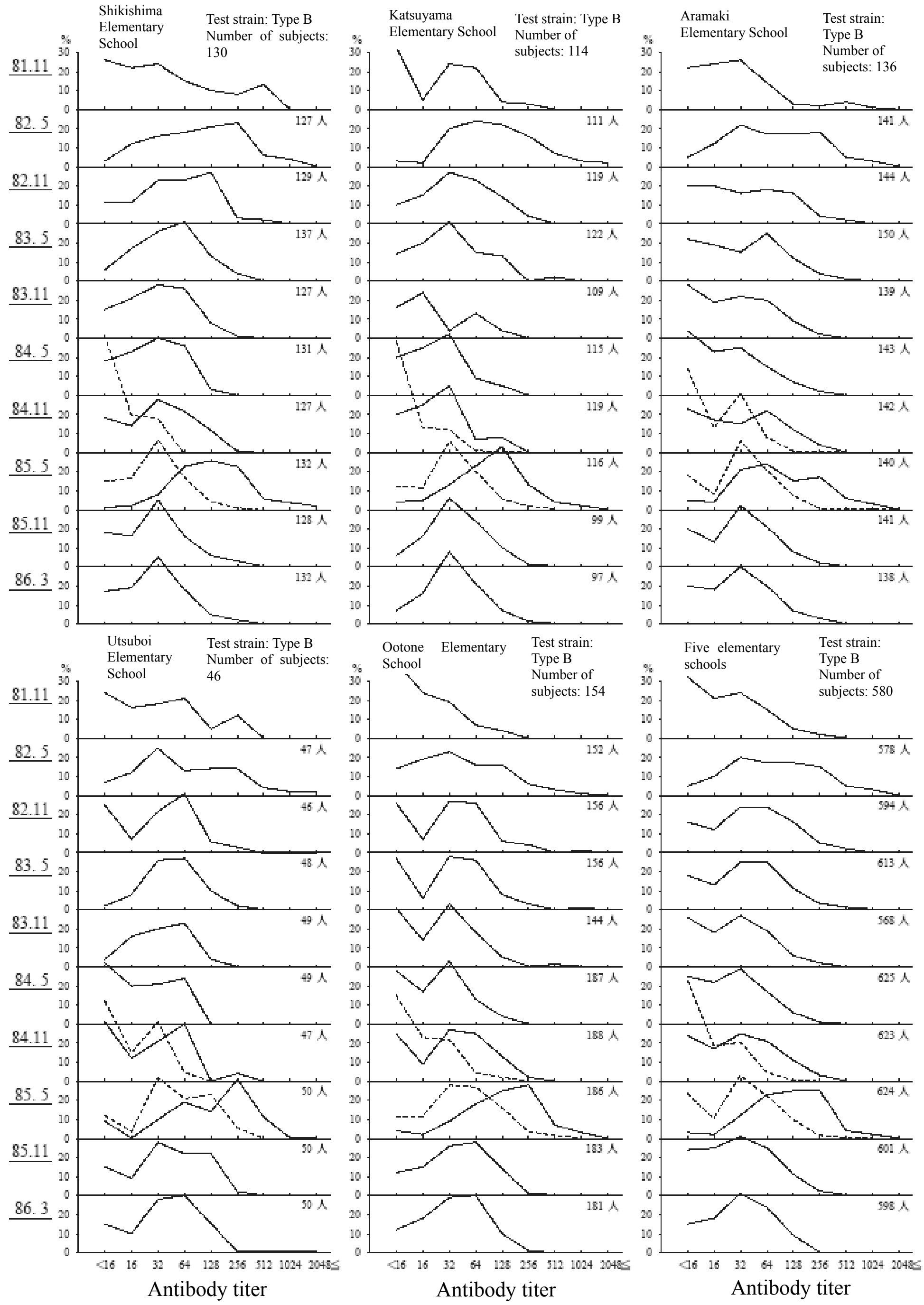


Figure 11. Distribution of Antibody Titers against Type B by School and Blood Sampling Period.

It is predicted with caution that the epidemic strain in the upcoming 1986–1987 winter season will be a relatively substantially mutated A/H_1N_1 strain and that a considerably large epidemic will occur. The figure suggests that a mutated strain, if it occurs, is likely to cause a large epidemic.

Figure 10 shows the change in the distribution of A/H_3N_2-specific antibody titers. A small epidemic occurred at Shikishima and Ootone elementary schools from February to March 1982, and a medium-sized epidemic occurred at all five schools the following year (January to February 1983). Three years later (November to December 1985) another epidemic occurred. Each epidemic was associated with a shift in the distribution curve of antibody titers to the right. The antibody titer-declining profiles were similar to those for the A/H_1N_1 strain. Antibody titers were well maintained.

However, antibody titers from November 1981 to May 1982 were measured with the use of two strains of A/Bangkok and A/Niigata. The latter is indicated with a dashed line. The epidemic was characterized by many subjects with a titer less than 16-fold. In this case, the distribution curve shifted to the right after the epidemic, but the number of infected persons appeared to be smaller than that during periods for which the pre-epidemic distribution curve had a peak of 32- to 64-fold. This issue together with type B is described later. It was unclear which strain more closely resembled the actual epidemic strain. Nevertheless, the latter pattern implies the distribution curve measured with a significantly mutated epidemic strain.

Finally, Figure 11 shows the change in the distribution curve of type B-specific antibody titers. The epidemic occurred from January to February 1982 and from January to February 1985. The general features of these changes were similar to those for type A. Measurements were made with B/Singapore from November 1981 to May 1985 and with B/USSR of November 1985 and March 1985. For the former measurements (the solid lines in the figure), the distribution of antibody titers after the epidemic (May 1982) had a peak of 32- to 64-fold. The subsequent changes were characterized by many subjects with a titer less than 16-fold, in contrast to type A. Given that the distribution of antibody titers after the epidemic (January to February 1985) showed a pattern similar to that observed for type A, the antibody titer against type B may be less likely to increase. It is unclear whether this was attributed to the nature of test strains or a small number of previous infections with influenza B in subjects. However, this is probably attributed to the latter because records on previous epidemics showed that influenza B epidemics were less frequent.

For the measurement in November 1984 and May 1985, two strains of B/Singapore and B/USSR were used. In Figure 11, the former is shown by the solid line, and the latter is shown by the dashed line. In the measurement with the latter, the proportion of subjects with a titer less than 16-fold was markedly high. The infection rate was 57.8% for the former and 51.3% for the latter. The titer measured with the former was higher by 6.5 percentage points. However, the relationship was not simple. The proportion of subjects with an increase in antibody titer of at least fourfold (the proportion of subjects with infection) was 64.3%. Of these, 69.7% had an increase in antibody titers against the two strains, 20.2% had an increase in the titer against B/Singapore alone, and 10.1% had an increase in the titer against B/USSR alone.

The antibody titer against B/Singapore was used for the subsequent investigation. Still, the results indicated that selection of test strains was an important issue. Nevertheless, when the proportion of subjects with an antibody titer of 16-fold or less was high, fluctuations of antibody titers within the range were less likely to be considered infection as long as infection was defined as an increase in antibody titer of at least fourfold.

2) Relationship between the absentee rate and the infection rate

Table 15 and Figure 12 show the relationship between absentees and infected persons during each epidemic period. Table 15 shows the epidemic period, epidemic strain, and the number of subjects from left to right. The number of subjects was determined at schools with evidence of epidemics. During the A/H_1N_1 epidemic from December 1983 to February 1984, Utsuboi Elementary School, one of the five designated schools, had only two infected persons, and these persons were excluded from the analysis.

Table 15. The Absenteeism Rate, Infection Rate, and Relationship between Absentees and Infected Persons During Each Epidemic.

Epidemic period	Epidemic strain	Number of subjects	Persons absent		Persons present			Absentee rate	Infection rate	Proportion of infected persons to persons absent	Proportion of infected persons to persons present	Proportion of persons who were infected but present (proportion of persons with inapparent infection)
			Uninfected persons	Infected persons	Infected persons	Uninfected persons	Infected persons (total)					
1982.1.16 to 1982.2.25	B	516 persons	91 persons	140 persons	117 persons	168 persons	257	44.8 %	49.8%	60.6%	41.1%	45.5%
1982.2.25 to 1982.3.16	A/H_3N_2	251*	19	24	41	167	65	17.1	25.9	55.8	19.7	63.1
1983.1.12 to 1983.2.17	A/H_3N_2	521	70	119	91	241	210	36.3	40.3	63.0	27.4	43.3
1983.12.12 to 1984.2.15	A/H_1N_1	516**	115	55	79	267	134	32.9	26.0	32.4	22.8	59.0
1985.1.10 to 1985.2.13	B	602	118	192	99	193	291	51.5	48.3	61.9	33.9	34.0
1985.11.18 to 1985.12.23	A/H_3N_2	591	66	175	140	210	315	40.8	53.3	72.6	40.0	44.4

* An epidemic occurred at two schools (Shikishima and Ootone elementary schools).

** An epidemic occurred at four schools (Shikishima, Katsuyama, Ootone, and Aramaki elementary schools).

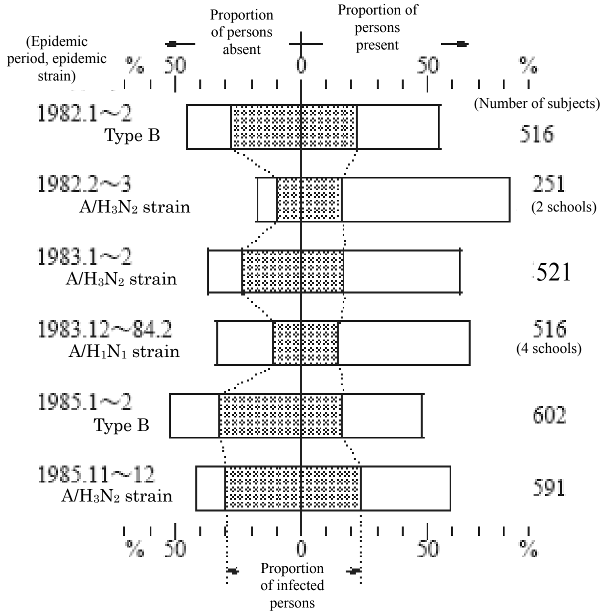


Figure 12. Relationship between the Proportion of Absentees and the Proportion of Infected Persons During Each Epidemic Period.

In the subsequent columns, the numbers of persons absent, persons present, and infected persons are shown. Here, the number of absentees was calculated on the assumption that those who were absent at least once during an epidemic period were absent because of influenza. No class was closed in the grade surveyed.

Calculation of the number of infected persons was based on persons with at least a fourfold increase in antibody titer from November to May of the following year (before and after the epidemic). The proportions of absentees and others calculated from those values are expressed as percentages in the right columns.

Figure 12 illustrates the relationship between absentees and infected persons. As indicated in the figure, infected persons accounted for only 60% to 70% of absentees even during epidemics with an absentee rate in elementary schools exceeding 5% or during middle-sized and large epidemics recognized as such by anyone. The proportion was even smaller during small or prolonged epidemics. Strangely, the proportion of persons who were infected but not absent was constant at about 20% of the total across epidemic periods. The proportion of persons with inapparent infection shown in the rightmost column of Table 15 was 35% to 45% of infected persons during middle-sized epidemics as described previously and about 60% during small epidemics. Attention should be paid to the presence of persons with inapparent infection accounting for about 20% of the total. These persons are likely to excrete viruses in schools and play an important role in the spread of the viruses. There seems to be a modest inverse correlation between the proportion of infected persons and the proportion of persons with inapparent infection, although the small number of epidemics precludes a definitive conclusion.

3) Infection rate by antibody titer

Table 16 shows the infection rate by antibody titer during each epidemic period. For a better understanding, the relationship between the antibody titer and the infection rate is graphically presented in Figure 13.

A review of these curves produced the following findings. The pattern of these curves is not closely related to the size of the epidemic assessed by the infection rate. As type B infection rate curves indicate, the difference in the antibody titer range of 64-fold or less is related to the distribution pattern of pre-epidemic antibody titers. A large proportion of persons with a titer of

16-fold or less is associated with the pattern of the 1985 influenza B epidemic relative to the 1982 epidemic. Curves with a concave at an antibody titer of 16-fold are seen when antigenicity of test strains is substantially different from that of epidemic strains. In particular, in the case of the A/H_3N_2 epidemic from November to December 1985, the measurement was made with A/Philippine. For the epidemic strain, there should clearly be a twofold difference in antibody titer (a shift by one test tube in terms of the test method). The curve can be made to overlap with other curves by shifting it parallel to the left by one scale.

Table 16. Infection Rate by Antibody Titer During Each Epidemic Period.

Antibody titer		<16	16	32	64	128	256	512	1024	2048≤	Total
1982.1.16 to 1982.2.15 B	Subjects	159	100	125	78	32	13	6	1	0	514
	Infected persons	108	60	62	26	1	0	0	0	0	257
	Infection rate (%)	67.9	60.0	49.6	33.3	3.1	0	0	0	0	50.0
1982.2.27 to 1982.3.16 A/H_3N_2	Subjects	31	23	50	60	73	30	5	2	0	274
	Infected persons	19	15	21	14	5	0	0	0	0	74
	Infection rate (%)	61.3	65.2	42.0	23.3	6.8	0	0	0	0	27.0
1983.1.12 to 1983.2.17 A/H_3N_2	Subjects	156	31	103	148	71	8	2	0	0	519
	Infected persons	129	16	42	20	3	0	0	0	0	210
	Infection rate (%)	82.7	51.6	40.8	13.5	4.2	0	0	0	0	40.5
1983.12.12 to 1984.2.15 A/H_1N_1	Subjects	51	43	128	164	97	23	10	0	0	516
	Infected persons	31	13	49	32	9	0	0	0	0	134
	Infection rate (%)	60.8	30.2	38.3	19.5	9.3	0	0	0	0	26.0
1985.1.10 to 1985.2.13 B	Subjects	316	112	135	30	5	1	0	0	0	599
	Infected persons	216	49	26	2	0	0	0	0	0	293
	Infection rate (%)	68.4	43.8	19.3	6.7	0	0	0	0	0	48.9
1985.11.18 to 1985.12.23 A/H_3N_2	Subjects	35	27	155	195	143	28	8	0	0	591
	Infected persons	32	19	112	116	33	3	0	0	0	315
	Infection rate (%)	91.4	70.4	72.3	59.5	23.1	10.7	0	0	0	53.3

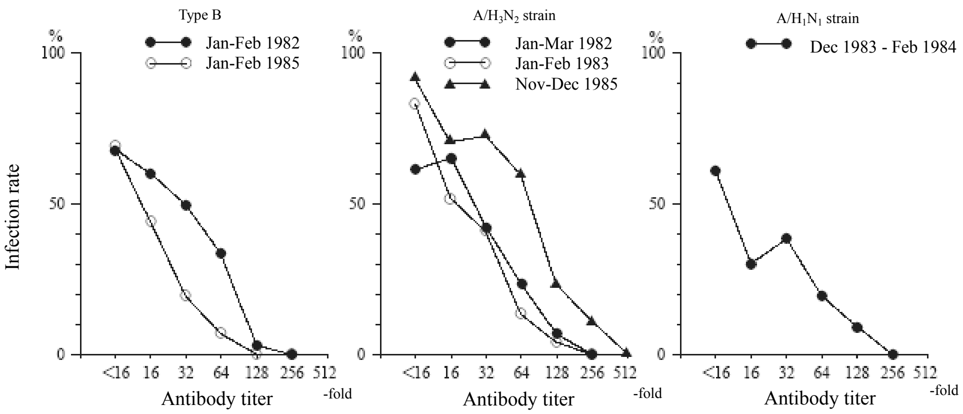


Figure 13. Infection Rate by Antibody Titer During Each Epidemic Period.

Only for the A/H_3N_2 epidemic from November to December 1985, the antibody titer scale was shifted to the left by one scale to make an adjustment, and the total number of subjects and the total number of infected persons for six epidemics were used to calculate the infection rate by antibody titer. The results are shown in Table 17 and graphically presented in Figure 14. The distribution curve of pre-epidemic antibody titers is shown by the dashed line in the figure. On the basis of our experience, I would say that the curve represents the distribution of antibody titers before a substantial scale of epidemic.

Table 17. Infection Rate by Antibody Titer on the Basis of Adjusted Means.

Antibody titer	<16	16	32	64	128	256
Number of subjects	775	464	736	623	306	83
Number of infected persons	554	265	316	127	21	0
Infection rate (%)	71.5	57.1	42.9	20.4	6.9	0
Number of subjects	1,239		1,359		389	
Number of infected persons	819		443		21	
Infection rate (%)	66.1		32.6		5.4	
Proportion of infected persons (%)	63.8		34.5		1.7	

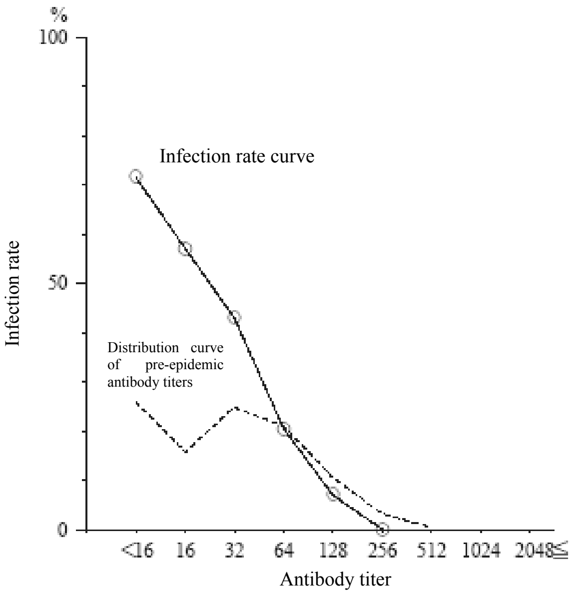


Figure 14. Antibody Titer Versus Infection Rate Curves on the Basis of Adjusted Means.

The figure shows that infection rarely occurs in persons with a natural infection-induced antibody titer of 128-fold or more. The infection rates in persons with antibody titers of 64-fold, 32-fold, 16-fold, and <16-fold were about 20%, 45%, 55%, and 70%, respectively. A rough analysis showed that persons with a titer of 16-fold or less accounted for 65% of all infected persons and that those with a titer of 32- to 64-fold accounted for 35%. However, this curve is only a model, and infection rate fluctuations within the range of ±10% are likely to occur frequently at each antibody titer.

It should be noted that these results were obtained from non-vaccinated children. As is well known, HI antibodies are IgG antibodies in blood and do not play a major role in protection against infection. The relationship between HI antibodies and IgA or cell immunity, which plays a major role in the protection against infection, is not clear. Thus, caution should be exercised when HI antibody titers are used as a measure of immunity.

Yet, the presence of HI antibodies in non-vaccinated children indicates a previous infection with the same type of viruses, and high HI antibody titers suggest a relatively recent history of infection. Therefore, HI antibody titers in this context are probably closely related to protection against infection. From this point of view, HI antibody titers of 64-fold or more appear to indicate the presence of substantially potent immunity, and titers of 16-fold or more suggest a history of infection.

In contrast, an inactivated vaccine selectively increases IgG levels in blood, and vaccine-induced increases in HI antibody titer cannot be interpreted in the same way as in the results described above. HI antibody titers in vaccinees are the result of previous infections and vaccine efficacy, which complicates the evaluation of HI antibody titers.

Specifically, HI antibody titers after a vaccination reflect one of the following:

1) Primary vaccine efficacy in persons without a previous infection
2) Natural antibodies in persons with a previous infection
3) Booster effect of vaccine in persons with a previous infection

It is difficult to distinguish among them. Thus, such a background should be taken into consideration when the relationship between HI antibodies and immunity is discussed in vaccination groups.

4) Previous infection and infection rate

To evaluate the effect of a past history of influenza infection on subsequent epidemics, the following survey was conducted. Persons were divided into groups according to previous infections with A/H_1N_1, A/H_3N_2, and type B, and the infection rates in these groups during subsequent epidemics were determined by measuring the change in HI antibody titer. Fortunately, we followed up the same children for five years and were able to examine the epidemics during the period. First, children with an antibody titer of at least 32-fold in November 1981 were considered to have a past history of infection, and those with a titer of 16-fold or less were considered to have no past history. According to the diagnostic criteria for infection described previously, persons with at least a fourfold increase in antibody titer before and after an epidemic were considered to have infection, and those with a twofold increase or less were considered to have no infection for calculation. Persons were divided into three groups according to virus type: A/USSR (A/H_1N_1: hereafter abbreviated as A1), A/Hong Kong (A/H_3N_2: hereafter abbreviated as A3), and type B. The relationship between past history and infection was investigated in these groups. The results are summarized in Table 18.

For a better understanding, Table 18 is graphically presented in Figure 15. Black rectangles indicate the proportion of persons with a past history or the proportion of infected persons. The width of rectangles indicates the proportion of persons divided according to the presence or absence of infection. This section describes individual types and then identifies a few problems.

(i) A/USSR strain

It is known that an A1 epidemic occurred when children were first graders (January to March 1981), and it is documented that different sizes of annual A1 epidemics occurred when they were preschool children (since 1978). This probably explains that a high proportion (92%) of children had a past history of infection with the A1 strain.

These children were exposed to the A1 epidemic from December 1983 to February 1984, which occurred more than three years after the previous one. At that time, the infection rate was 53.7% among those without a past history of infection and 21.7% among those with a past history of infection. This suggests that immunity was well maintained over a period of three years.

(ii) A/Hong Kong strain

In November 1981, 62.8% had a past history of infection with the A3 strain and antibodies. Although the epidemic from January to March 1982 was primarily attributed to type B, antibody testing at that time revealed a small A3 epidemic at two of the five designated schools (Shikishima Elementary School and Ootone Elementary School). Examination of absenteeism curves suggested that a small A3 epidemic might occur after the influenza B epidemic at 14 of 37 schools in the city. Thus, a group of Shikishima Elementary School and Ootone Elementary School was separated from the other three schools in Table 18.

A full-scale A3 epidemic occurred from January to February 1983, followed three years later by an epidemic from November to December 1985. Analysis of Shikishima Elementary School and Ootone Elementary School affected by the 1982 epidemic showed a substantial difference in the infection rate during the 1982 small epidemic between children with a past history of infection and those without. The epidemic had a significant effect on the infection rate during the epidemic the following year. The infection rate was 49.7% among those who were not infected the previous year but only 8.5% among those who were infected the previous year.

Past history of infection had also a significant effect during the epidemic three years later (November to December 1985). To highlight the trend at all five schools, the overall results, excluding those of the small epidemic from February to March 1982, are relisted in Table 19. As shown in this table, the infection rate from November to December 1985 was 67% among those without infection three years earlier and 34% among those with infection, and the ratio was about 2:1.

Over the course, 1 of 506 children was infected during all epidemics, and 2 children were not affected by any of the epidemics. All children appeared to be infected with the same type of virus one to three times until they graduated from elementary school.

(iii) Type B

Influenza B epidemics occurred from January to March 1982 and from January to February 1985. Another influenza B epidemic occurred before the start of the survey (March to May 1980), and persons with a past history in November 1981 were probably infected at that time. Thus, the epidemic from January to March 1982 occurred two years after the previous epidemic, and the infection rate was 33.6% among those with a past history and 59.4% among those without. Three years later (during the epidemic from January to March 1985), the infection rate was 36.0% among those who were infected in 1982 and 57.0% among those who were not.

Figure 16 shows the infection rate, absentee rate, and proportion of persons with fever during the epidemic, with stratification according to the presence or absence of a past history of infection. There was no difference in the absentee rate or the proportion of persons with fever between groups.

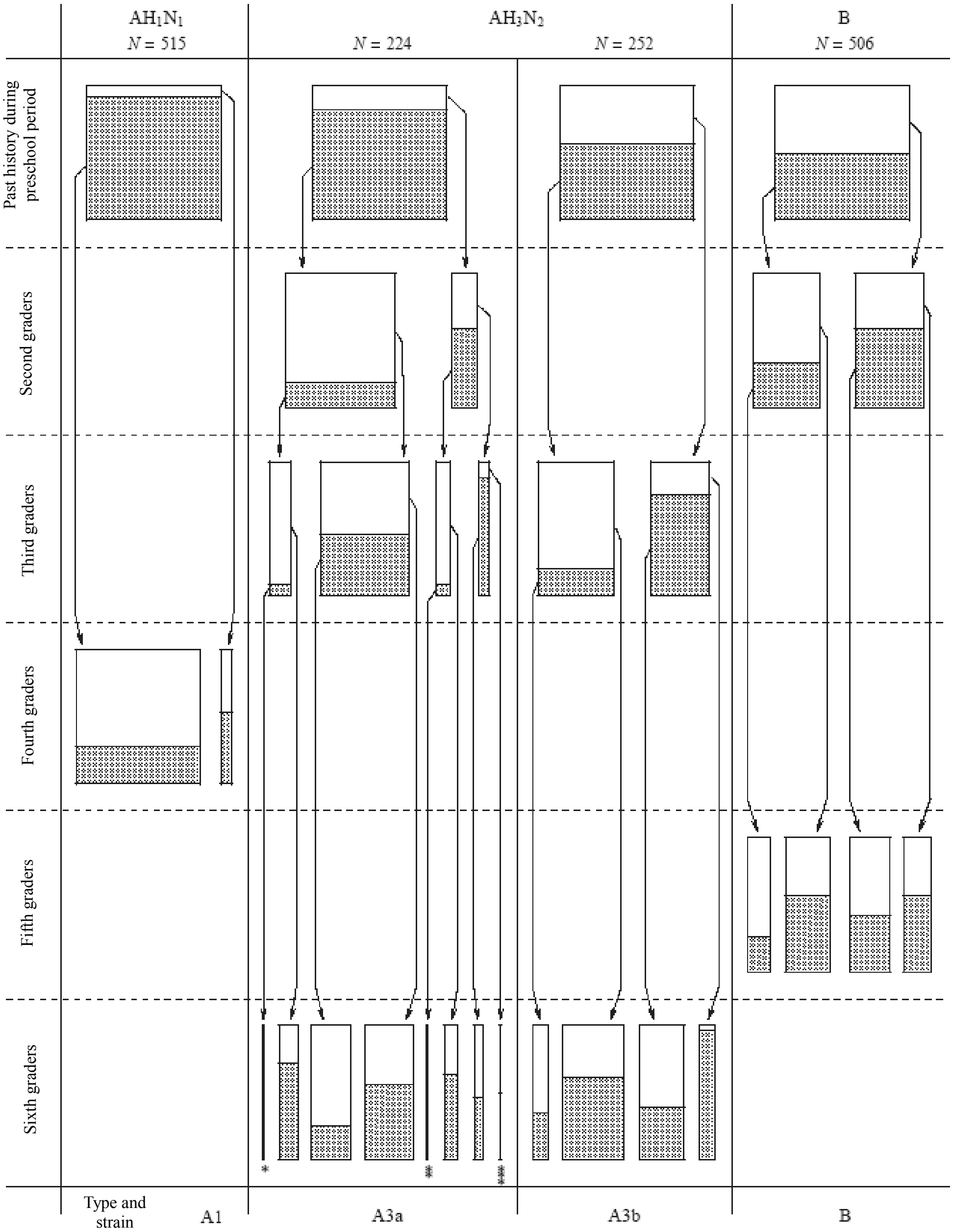
Figure 17 shows the relationship between previous infection with type B and subsequent epidemics. This is prepared by adding values to a part (type B) of Figure 15 for better understanding.

Table 18. Relationship Between Previous Infection and the Infection Rate.

Virus type	School	Nov 1981 blood sampling: Past history	Nov 1981 blood sampling: Number of persons (%)	Jan to Mar 1982: Infection	Jan to Mar 1982: Number of persons	Jan to Feb 1983: Infection	Jan to Feb 1983: Number of persons	Dec 1983 to Feb 1984: Infection	Dec 1983 to Feb 1984: Number of persons	Jan to Feb 1985: Infection	Jan to Feb 1985: Number of persons	Nov to Dec 1985: Infection	Nov to Dec 1985: Number of persons
A/ USSR (A1)		Y	474 (92.0)					Y	103				
								N	371				
		N	41 (8.0)					Y	22				
								N	19				
		Total	515					Y	125				
								N	390				
		Infection rate (%)						24.3					
A/ Hong Kong (A3)	Shikishima and Ootone elementary schools among designated schools	Y	183 (81.7)	Y	35	Y	3					Y	1
												N	2
						N	32					Y	23
												N	9
				N	148	Y	67					Y	17
												N	50
						N	81					Y	45
												N	36
		N	41 (18.3)	Y	24	Y	2					Y	0
												N	2
						N	22					Y	14
												N	8
				N	17	Y	15					Y	7
												N	8
						N	2					Y	1
												N	1
		Total	224	Y	59	Y	87					Y	108
				N	165	N	137					N	116
		Infection rate (%)		35.8		38.8						48.2	
	Aramaki, Katsuyama, and Utsuboi elementary schools		142 (56.3)			Y	29					Y	10
												N	19
						N	113					Y	69
												N	44
			110 (43.7)			Y	83					Y	32
												N	51
						N	27					Y	26
												N	1
		Total	252			Y	112					Y	137
						N	140					N	115
		Infection rate (%)				44.4						54.4	
B	All five designated schools	Y	250 (49.4)	Y	84					Y	22		
										N	62		
				N	166					Y	95		
										N	71		
		N	256 (50.6)	Y	152					Y	63		
										N	89		
				N	104					Y	59		
										N	45		
		Total	506	Y	236					Y	239		
				N	270					N	267		
		Infection rate (%)		46.6						47.2			

Table 19. Relationship Between Past History of Infection and the Infection Rate (relisted).

Virus type	School	Nov 1982 blood sampling: Past history	Nov 1982 blood sampling: Number of persons (%)	Jan to Feb 1983: Infection	Jan to Feb 1983: Number of persons	Dec 1983 to Feb 1984: Infection	Dec 1983 to Feb 1984: Number of persons	Jan to Feb 1985: Infection	Jan to Feb 1985: Number of persons	Nov to Dec 1985: Infection	Nov to Dec 1985: Number of persons
A/ Hong Kong	All five designated schools	Y	305 (62.8)	Y	61					Y	1
										N	2
				N	244					Y	23
										N	9
		N	181 (37.2)	Y	140					Y	17
										N	50
										Y	45
				N	41					N	36
		To tal	486	Y	201					Y	0
				N	285					N	2
		Infection rate (%)		41.4						53.3	



* Two of three persons were infected. ** None of two persons was infected. *** One of two persons was infected.

Figure 15. Relationship Between Past History of Infection with Specific Type and the Infection Rate.
(The width indicates the proportion of subjects, and black boxes indicate the proportion of infected persons.)

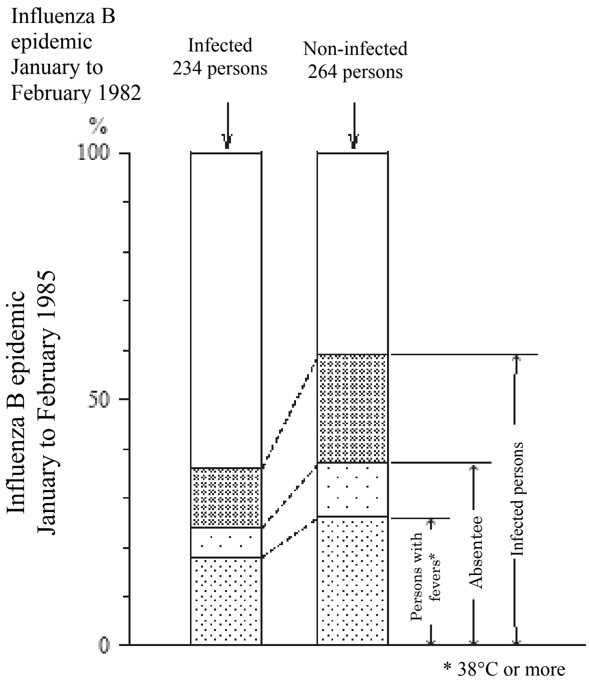


Figure 16. Proportion of Infected Persons, Absentee Rate, and Proportion of Persons with a Temperature of 38°C or More During the 1985 Influenza B Epidemic in Persons with or without Infection During the 1982 Epidemic.

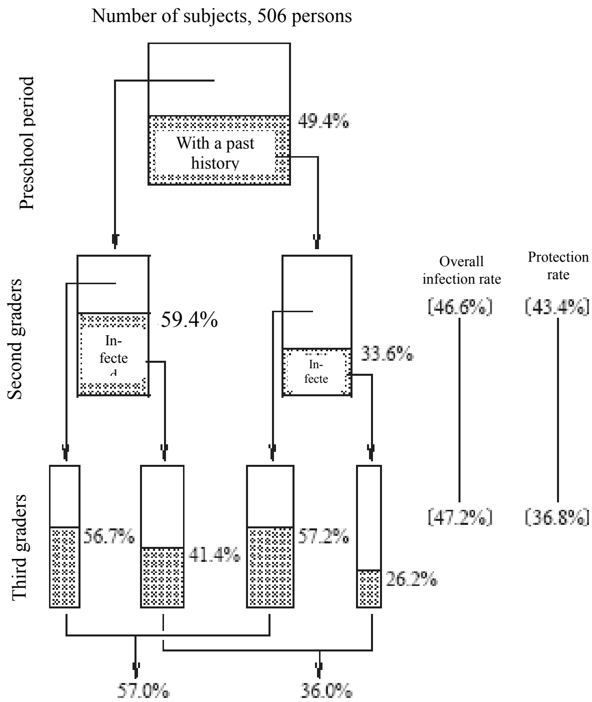


Figure 17. Relationship Between Past History of Infection with Influenza B and the Infection Rate.

As a model, a very understandable relationship is presented. This model is not applicable to all types of viruses or all epidemic periods but appropriately shows the basic relationship. There were 506 subjects, about half of whom had a past history. Before the subjects (children surveyed) became first graders, they were possibly exposed to an influenza B epidemic at the age of two years and a triple epidemic (A1, A3, and type B) at the age of five years. When they were first graders, A1 and A3 epidemics occurred, followed by a small influenza B epidemic from mid March to mid May. The effect of the epidemic at the age of five years appeared to be most significant.

Figure 17 shows infection rates during epidemics occurring when they were second graders (two years later) and fifth graders (another three years later) in groups divided according to the presence or absence of infection.

When they were divided into groups according to the presence or absence of a past history of infection, the infection rate was 59.4% among those without a past history and 33.6% among those with a past history. When they were further divided into groups during the subsequent epidemic according to the presence or absence of infection in two groups, the infection rates in those without previous infection were 56.7% and 57.2%, with no substantial difference, suggesting the significance of lack of infection during the previous epidemic. The infection rate was 41.1% in persons who were infected during the previous epidemic but no past history and 26.2% in persons who were infected during the previous epidemic and a past history, indicating that the infection rate tended to be lower in persons with repeated infections.

The infection rate in persons with both a past history and infection was less than half that in those without previous infection. As a whole population, however, the ratio of the infection rate in persons with previous infection to the infection rate in those without was about 5:3 when they were second graders and when they were fifth graders. The overall infection rates during the two epidemic periods were 46.6% and 47.2% with no substantial difference between the periods. The protection rates were 43.4% and 36.8% with a difference of only 6.6 percentage points.

As described previously, such clear relationships were found only with influenza B viruses, which are believed to undergo relatively minor mutations. In the case of influenza A viruses, there are essentially similar relationships, but modification by antigenic mutations of epidemic viruses may result in more complicated changes. Whatever the case may be, this figure shows how children acquire immunity against influenza.

(iv) Infection protection rate by past history

The results described above show that previous infection with any type and strain of virus generally has the effect of reducing the infection rate, that is, an immune effect. The immune effect is clearly maintained without a vaccination and even when viruses continue to mutate.

On the basis of a sufficient number of subjects for comparison and a certain trend in the infection rate, we investigated the relationship between the presence or absence of infection during the previous epidemic and the infection rate during the subsequent epidemic period.

Table 20 compares six epidemics with a focus on the presence or absence of infection during previous epidemics. During each of the epidemics, the infection rate was clearly lower in persons who were infected during the previous epidemic than in persons who were not. When persons were further classified according to the presence or absence of infection during the second previous epidemic, the infection rate clearly tended to be lower in persons with repeated infections.

As shown in the rightmost column of Table 20, the protection rate for type A_3 calculated by the formula of the vaccine efficacy rate was about 80%, 70%, and 50% at one, two, and three years after the previous epidemic, respectively.

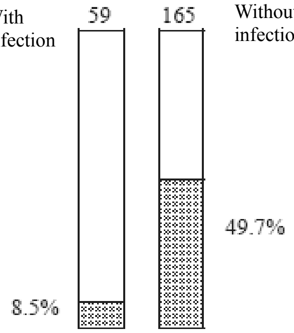
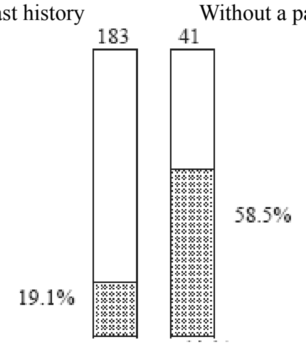
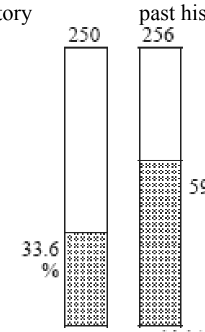
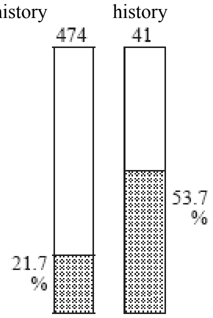
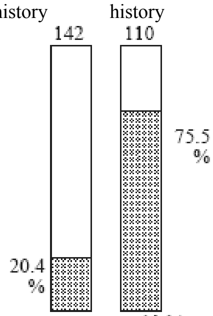
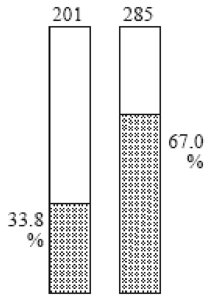
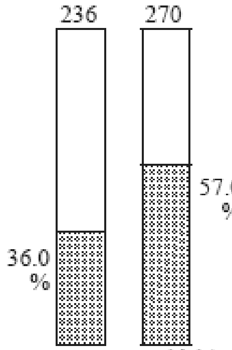
(v) Number of years elapsed and the infection rate

Figure 18 is based on Tables 18, 19, and 20; persons are divided into groups with a past history or infection during the previous epidemic and those without, and data are presented for each type and the interval between epidemics (number of years). Past history in this context means infection during epidemics before the start of the group survey activities. As described previously, persons with an HI antibody titer of at least 32-fold in November 1981 were considered to have a past history, and those with a titer of 16-fold or less were considered to have no past history. The reference time point for calculation of epidemic interval was the 1981 winter epidemic for type A1 and the mixed epidemic from March to May 1980 for type A3 and type B. This was based on records by the prefectural institute for public health.

Table 20. Infection Rate by the Number of Previous Epidemic Infections and the Rate of Protection by Previous Infection.

Virus type	School group	Time of previous epidemics	Epidemic period at elementary schools in Maebashi City	Infection rate	With infection during the previous epidemic	Without infection during the previous epidemic	By previous epidemic infection	
							Interval between epidemics	Protection rate
		Year		%	%	%	Years	%
A/USSR	Five designated schools	1981 1980	Dec 1983 to Feb 1984	24.3	21.7	53.7	3	59.6
A/Hong Kong	Two of five designated schools*	1982 1978	Jan to Mar 1982	35.8	19.1	58.5	2	67.4
	Two of five designated schools*	1982 1980 1978	Jan to Feb 1983	38.8	8.5	49.7	1	82.9
	Five designated schools	1983 1982 1981 1978	Nov to Dec 1985	53.3	33.8	67.0	3	49.6
B	Five designated schools	1980 1977	Jan to Mar 1982	46.6	33.6	59.4	2 (5)	43.4
	Five designated schools	1982 1980 1977	Jan to Feb 1985	47.2	36.0	57.0	3	36.8

* The epidemic occurred only at two schools (Shikishima Elementary School and Ootone Elementary School).

Interval from the previous epidemic	A/H_1N_1 (A/USSR)	A/H_3N_2 (A/Hong Kong)	B
One year later		(Numerals on the bar chart indicate the number of subjects.)  Epidemic from Jan to Feb 1983 (Two of the five designated schools: Shikishima and Ootone Elementary Schools)	
Two years later		 Epidemic from Feb to Mar 1983 (Two of the five designated schools: Shikishima and Ootone Elementary Schools)	 Epidemic from Jan to Feb 1982 (Five designated schools)
Three years later	 Epidemic from Dec 1983 to Feb 1984 (Five designated schools)	 Epidemic from Jan to Feb 1983 (Three of the five designated schools: Katsuyama, Aramaki, and Utsuboi Elementary Schools)  Epidemic from Nov to Dec 1985 (Five designated schools)	 Epidemic from Jan to Mar 1985 (Five designated schools)

Note 1: Persons with a past history in this context indicate those who had infection during epidemics before 1980, specifically those who had an HI antibody titer of at least 32-fold in blood collected in November 1981. Persons without a past history indicate those with a titer of 16-fold or less. Epidemic periods and types before 1981 are based on records by the prefectural institute for public health.

Note 2: Persons with infection in this context indicate those who had an increase in antibody titer of at least fourfold during the previous epidemic, and persons without infection indicate those who had a change in antibody titer by twofold or less.

Figure 18. Relationship between the Presence or Absence of Past History and Infection during Previous Epidemics and the Infection Rate.

Numerals above the bar charts in the figure indicate the number of subjects, and percentages on both sides indicate the infection rate. Among the five schools, one group of two schools and the other group of three schools remained unchanged.

Under the circumstances, analysis of the relationship between the presence or absence of a past history and previous infection and the infection rate revealed that children without a past history or infection during the epidemic three years earlier had an infection rate almost twice that in those with a past history and infection. As expected, when the interval was shorter (two or one vs. three years), the infection rate in children with a past history and infection was significantly lower, and the infection rate in children without a past history or previous infection was also slightly lower. Consequently, the difference tended to increase.

The epidemic one year later was a small, local epidemic occurring in the city. Persons with a past history (antibody carriers) had an infection rate of only 8.5%, whereas persons without a past history (those without antibodies) had an infection rate of 49.7%, which was 5.8 times that for antibody carriers.

These results are summarized as follows. The infection rate in antibody carriers was about 10% during the same type of epidemic one year later, about 25% during the epidemic two years later, and about 30% during the epidemic three years later. The infection rate in persons who were not infected during the previous epidemic was approximately 50% during the epidemic one year later, 60% two years later, and about 65% three years later.

5) Change in the distribution of antibody titers in the population

This section describes the general features of HI antibody titers used in the survey, specifically a few findings on how antibody titers changed over time in association with epidemics. Needless to say, the change in antibody titers and the pattern of immune response during epidemics always differ substantially among individuals. This section does not take these issues into consideration but focuses on the results of the investigation of herd immunity.

In Table 21, persons at the five designated schools were divided into two groups, that is, persons who were infected during the influenza B epidemic from January to February 1982 and those who were not, and the change in the distribution of antibody titers measured four times over a period of two years, a period starting before the epidemic, was shown. The table includes persons for whom all the four antibody titer measurements were available. It was by coincidence that the numbers of subjects in the infected group and the uninfected group were the same (257 persons). The values are graphically presented in Figure 19.

Table 21. Change in Antibody Titer over Time in Persons Infected with Influenza B and Uninfected Persons.

Group	Blood sampling period	Antibody titer	<16	16	32	64	128	256	512	1024	2048 fold	Mean
Infected persons (257)	Nov 1981	N	108	60	62	26	1					24.0
		%	42.0	23.4	24.1	10.1	0.4					
	May 1982	N			34	51	58	69	29	12	4	27.2
		%			13.2	19.8	22.6	26.9	11.3	4.7	1.6	
	Nov 1982	N	10	20	59	78	65	18	5	2		26.0
		%	3.9	7.8	23.0	30.4	25.3	7.0	2.0	0.8		
	May 1983	N	17	25	69	92	38	12	3	1		25.6
		%	6.6	9.7	26.9	35.8	14.8	4.7	1.2	0.4		
Uninfected persons (257)	Nov 1981	N	51	40	63	52	31	13	6	1		25.2
		%	19.8	15.6	24.5	20.2	12.1	5.1	2.3	0.4		
	May 1982	N	35	54	72	42	36	12	4	2		25.2
		%	13.6	21.0	28.0	16.3	14.0	4.7	1.6	0.8		
	Nov 1982	N	79	52	61	45	13	7				
		%	30.7	20.2	23.7	17.5	5.1	2.7				
	May 1983	N	90	53	63	36	12	3				24.4
		%	35.0	20.6	24.5	14.0	4.7	1.2				

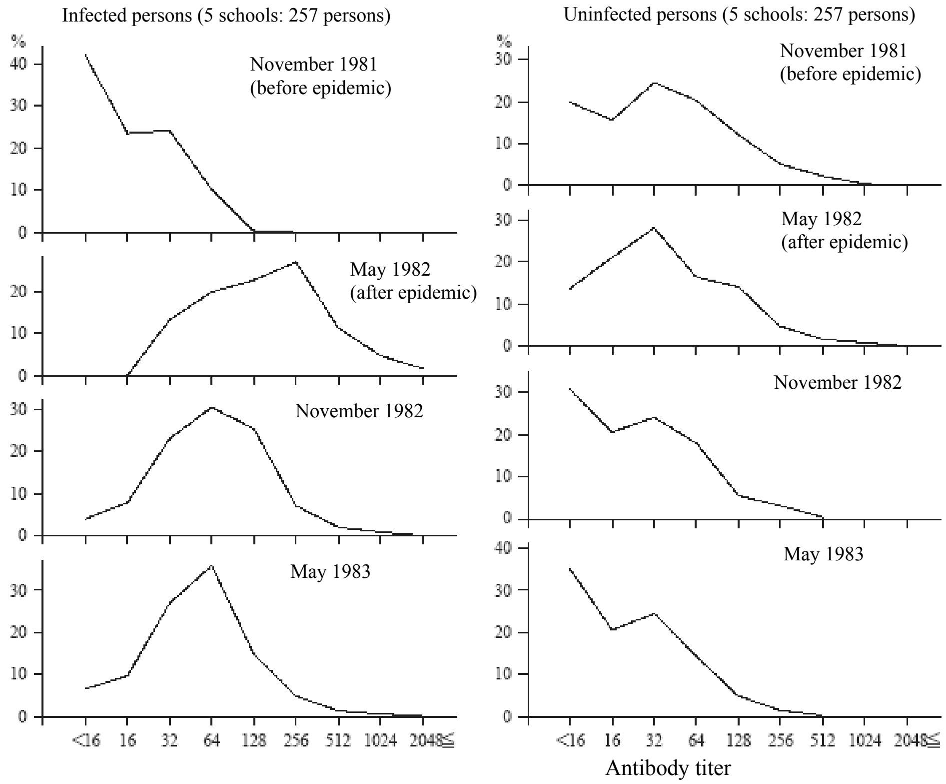


Figure 19. Change in Antibody Titer over Time in Persons Infected with Influenza B and Uninfected Persons.

The figures on the left show the change in the distribution of antibody titers in the infected group before and after the epidemic and thereafter. The figures on the right show the change in the uninfected group during the same period.

The pattern of the distribution of antibody titers after the epidemic in the uninfected group indicates that they were influenced by the epidemic to some extent. This is because an at least fourfold increase in antibody titer was considered a sign of infection. Actually, the uninfected group included some persons who were infected but did not show an increase in antibody titer by a factor of four or more. However, those persons are disregarded here.

When you look at the figures from the upper left to the lower left and then from the upper right to the lower right, you may feel as if you were looking back to the first curve of the distribution of antibody titers. Although these are obviously different groups, it is empirically estimated on the basis of the change in the distribution of antibody titers that it may take approximately three years for the distribution pattern of antibody titers after the epidemic on the second chart from the top on the left (bell-shaped curve with a peak antibody titer of 256-fold) to return to the original pattern characterized by a downward-sloping curve before the epidemic. In other words, in three years, the distribution of antibody titers is likely to return to one with which a similar scale of epidemic may occur again. Nevertheless, it is evident that the distribution of antibody titers is not the sole determinant of the occurrence and scale of epidemics. One of the facts supporting this estimate is as follows. In the analysis of the mean decrease in antibody titer against A1 type, as expected, the percent reduction is greater in persons with higher antibody titers. The relationship is exponential within the common range of HI antibody titers, and the semilogarithmic plot shows a linear relationship.

For influenza B, the mean antibody titer was calculated from Table 21, and a decline curve was drawn on a semilogarithmic plot by plotting the calendar year on the abscissa. The plot indicates that the half-life was approximately 10 months and that it took approximately two years seven to eight months to return to the original condition before the epidemic. These values are in good agreement with empirical estimates.

We planed to performe the same investigation on other types later. To begin with, we investigated the distribution of pre-epidemic antibody titers against A3 type in infected persons and uninfected persons during each epidemic.

The results are shown in Figure 20. Details are omitted. The mean antibody titer differs by $2^{0.6}$ to $2^{1.8}$ between the two groups. In a comparison of the influenza B epidemic (January to February 1982) and the A3 type epidemic (November to December 1985) at the five designated schools, there was a substantial difference in the distribution pattern of antibody titers, but the differences in the mean antibody titer between the two groups were not remarkable ($2^{1.2}$ and $2^{1.0}$). In short, on the assumption that the potency of antibodies was the same, the uninfected group appeared to have antibody levels about twice those in the infected group. The conditions appeared to be similar regardless of type, but this issue requires further investigation. We would like to present results if an opportunity occurs.

As described repeatedly, it is not appropriate to use numerical values calculated from HI antibody titers to generalize a variety of influenza epidemics that are influenced by a large number of factors. Nevertheless, it is fairly reasonable to use HI antibody titers in the analysis of herd immunity in influenza epidemics.

6) Absentee rate and the proportion of persons with a temperature of 38cal values calculated from HI antibody titers to generalize a

Table 22 shows the absentee rate and the proportion of persons with a temperature of 38°C or more by pre-epidemic antibody titer in infected persons during each epidemic period. As shown in this table, higher antibody titers were not always associated with lower rates of absentees or a lower proportion of persons with fever. As a whole, however, the absente rate and the proportion of persons with fever tended to be lower when the antibody titer was higher.

It was reported previously that analysis of data on the A3 epidemic from January to February 1983 and the A1 epidemic from December 1983 to February 1984 found no correlation between the pre-epidemic antibody titer in infected persons and the absentee rate or the proportion of persons with fever. However, on the basis of an investigation of all epidemics, corrections have to be made as follows.

As described previously, the infection rate tended to decrease as the pre-epidemic antibody titer increased. Among infected persons, the absentee rate and the proportion of persons with a temperature of 38°C or more also tended to decrease similarly. When persons with an antibody titer of 16-fold or less were considered antibody non-carriers and those with a titer of at least 32-fold were considered antibody carriers, the absentee rate was 67.0% for the former and 55.5% for the latter, and the proportion of persons with fever was 49.1% for the former and 38.0% for the latter. In other words, the absentee rate and the proportion of persons with fever were approximately 10% lower in infected persons with a past history than in persons without a past history.

In the case of elementary schoolchildren, however, most persons with a temperature of 38°C or more must be absentees, and thus there should be no clear correlation between the proportion of persons with a temperature of 38°C or more in absentees with infection and the pre-epidemic antibody titer. There was presumably no difference in the distribution of the degree of disease conditions after infection and the onset of disease, regardless of pre-epidemic antibody titers. In short, the degree of disease conditions is not determined solely by the antibody titer.

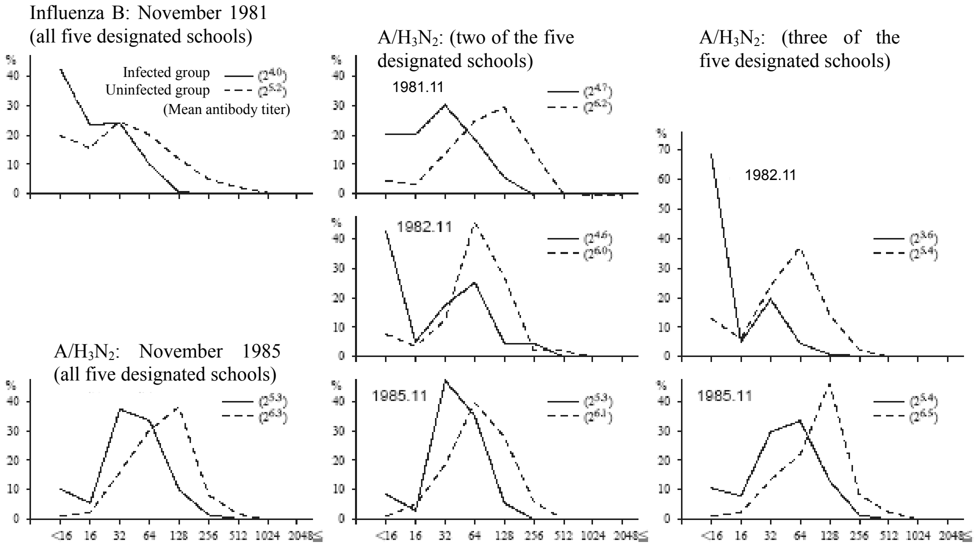


Figure 20. Distribution of Pre-epidemic Antibody Titers in Infected Persons and Uninfected Persons during Influenza B and A/H_3N_2 Epidemics.

Table 22. Absenteeism Rate and the Proportion of Persons with Fever (38°C or more) in Infected Persons by Pre-epidemic Antibody Titer during Each Epidemic Period.

Infected persons		Absenteeism rate					Proportion of persons with fever				
Antibody titer		<16	16	32	64	128≦	<16	16	32	64	128≦
Jan to Feb 1982 B	Number of subjects	114	66	62	29	0	114	66	62	29	0
	Number of persons absent or with fever	87	42	41	15	0	62	26	21	6	0
	%	76.3	63.6	66.1	51.7	0	54.4	39.4	33.9	20.7	0
Feb to Mar 1982 A/H3N2	Number of subjects	19	13	21	14	5	19	13	21	14	5
	Number of persons absent or with fever	16	8	16	11	3	12	7	12	5	2
	%	84.2	61.5	76.2	78.6	60.0	63.2	53.8	57.1	35.7	40.0
Jan to Feb 1983 A/H3N2	Number of subjects	129	16	42	20	3	129	16	42	20	3
	Number of persons absent or with fever	80	7	18	13	1	64	4	16	10	1
	%	62.0	43.8	42.9	65.0	33.3	49.6	25.0	38.1	50.0	33.3
Dec 1983 to Feb 1984 A/H1N1	Number of subjects	30	13	50	31	9	30	13	50	31	9
	Number of persons absent or with fever	18	6	31	9	4	10	3	20	5	1
	%	60.0	46.2	62.0	29.0	44.4	33.3	23.1	40.0	16.1	11.1
Jan to Feb 1985 B	Number of subjects	110	62	102	49	14	110	62	102	49	14
	Number of persons absent or with fever	77	36	66	26	7	57	27	40	27	7
	%	70.0	58.1	64.7	53.1	50.0	51.8	43.5	39.2	55.1	50.0
Nov to Dec 1985 A/H3N2	Number of subjects	30	19	113	116	35	30	19	113	116	35
	Number of persons absent or with fever	25	14	63	59	14	22	11	45	43	11
	%	83.3	73.7	55.8	50.9	40.0	73.3	57.9	39.8	37.1	31.4

4. Summary and discussion

1) Usefulness of the absentee rate in elementary schools as a measure of epidemics

There are a variety of measures for influenza epidemics including the number of closed classes, the number of cases of influenza-like illness, reported mortality rate, excess mortality, the number of patients reported by physicians, the number of viral samples provided, and the number of epidemic virus strains detected. The first two data are official information by the Ministry of Health and Welfare and disseminated widely by the mass media. In general, however, these measures are relative ones. This cannot be helped because influenza is a disease that produces no specific clinical symptoms.

The number of closed classes has been frequently used to compare epidemics among relatively small areas. It is, however, not very meaningful because the requirements for class closures differ considerably depending on the area, epidemic period, and school.

Individual areas have their criteria for implementation of class closure. In many areas, a class is generally closed for five days or more if the number of absentees exceeds 20% of enrolled children, and the criteria are described in many textbooks. However, classes are usually closed simultaneously just before the epidemic peaks, and there is often a substantial time lag from the start of the epidemic to the closure. (See Appendix 3, which is related to a class closure survey at Aramaki Elementary School reported at a regular group meeting. This is referred as an example related to this discussion. The efficacy of class closure in influenza epidemics is controversial, and this issue is considered a challenge for the future at the group meeting.) With consideration of these issues, we discussed the best procedure to monitor epidemics in a relatively small area like Maebashi City and selected the daily rate of absentees at elementary schools. Many schools routinely examine the daily number of absentees. We believed that, by asking schools to report the data for analysis, we would be able to achieve the goal without placing much burden on the schools.

Elementary schoolchildren represent a very limited part of the population in the city. From a geographical point of view, however, the location of elementary schools well reflects the features of individual areas of the city, and the absentee rate in elementary schools appeared to be better than that in kindergartens, junior high schools, or high schools in that it provided more reliable data with less bias.

A type of epidemic curve was obtained by plotting the calendar day on the abscissa against the daily rate of absentees on the ordinate. During influenza epidemics, smooth, bell-shaped epidemic curves were often obtained. The criterion for the absentee rate of 2% facilitated observation of the epidemic period and the epidemic pattern. The use of the highest rate of absentees and the epidemic period allowed rough estimation of the epidemic scale.

Some may argue that the absentee rate of 3% or 3.5% may be a better criterion. We support the usefulness of the 2% level when not only influenza but also other infectious diseases are considered for the purpose of school health. Methods for the analysis of epidemics with the use of absentee rates or curves as a measure have been extensively used for years. However, many analysis were performed during a single year or a short period in a small area, such as a single school. In many recent reports, those variables and the change in HI antibody titers were analyzed to evaluate the vaccine efficacy. The usefulness has already been proven.

However, there has been no report in which the absentee rate was followed up for five years or more in a wide area comparable to Maebashi City. Moreover, our survey is unique in that investigation was performed in an area without influenza vaccination.

The characteristics of the absentee rate as a measure of epidemics and considerations in the use are detailed in a book written by Tadao Sonoguchi.[1] However, many of the survey results referred to in his book are related to vaccinated areas. Nonetheless, many of our findings are surprisingly in agreement with those survey results.

When drawing epidemic curves on the basis of influenza-related absentees, we noted the following issues in association with epidemics in the city. During our observation period, influenza epidemics usually started with an epidemic at a few schools, followed sooner or later by simultaneous initiation of epidemics at all other schools. It was impossible to identify the geographical infection route from the first couple of schools to the rest of the epidemic schools. Before school epidemics started, patients with influenza-like illness were usually found in different regions of the city. In the early stage of epidemics, the infection route between families, schools, or classes was identifiable in some cases. Before long, those events were found simultaneously across the city, and epidemics swept through the city. When school epidemics ended, the epidemics in the city were almost over.

This is a well-known phenomenon that shows epidemic features during the period called the interpandemic period.[2] With this regard, we confirmed that epidemic curves for elementary schools well reflected epidemics in the city by using the Influenza-like Illness Surveillance Report compiled by the Gunma Medical Association as a reference. However, we were not able to investigate in detail the temporal relationship between city epidemics and school epidemics because the prefectural reports were monthly reports. In this type of surveillance program implemented by all members of a medical association, it seems difficult to issue weekly reports.

For comparison with nationwide epidemics, influenza epidemic information by the Ministry of Health and Welfare was used. Epidemic curves overlapped each other and were in surprisingly good agreement with respect to the size of the epidemic and pattern. Macroscopically, it was quite unlikely that abnormal epidemic situations developed in Maebashi City, a non-vaccinated area. In short, mass vaccinations of schoolchildren do not have a substantial effect on epidemics in elementary schools.

2) Effect of discontinuation of mass vaccination on epidemics in the city

As described previously, the current policy on influenza vaccinations and control may be summarized into the mass vaccination of schoolchildren for the construction of a shield, called "Theory of school children breakwater" in Japan. The question arose whether the policy was really effective. We believed that vaccinations should be resumed soon after they were found to be effective.

Although there were limited data and means available, comparison of the incidence of influenza-like illness by area, clinical visits covered by the National Health Insurance by area, and excess mortality by area demonstrated that Maebashi City with discontinuation of mass vaccination did not have more patients with influenza, greater health care costs, or higher mortality rates in older individuals and high-risk individuals than vaccinated areas.

Through these activities, however, we noticed an insufficient surveillance system for influenza epidemics. It has been 14 years since the current influenza HA vaccine was put to practical use. To achieve high vaccination rates, considerable effort and costs were used annually. Meanwhile many studies were conducted, most of which concluded that vaccinations were effective but not satisfactory. Therefore, some suggested a later vaccination period (December to January) or an increase in the number of doses to three.[3,4]

We understand the difficulties in epidemiological surveys. The Ministry of Health and Welfare, which should have conducted such surveys earlier, recently started organizational reevaluations at last. We wonder why the Ministry sat still and did nothing for so long. Nonetheless, the Ministry has started reevaluations and should draw convincing conclusions.

The results of 3-A and B showed that epidemics in Maebashi City, a non-vaccinated area, were not essentially different from those in vaccinated areas. We believe that the strategy to prevent local epidemics by using schoolchildren as a shield is proven wrong.

3) Vaccine efficacy in terms of the absentee rate

During influenza epidemics, other viruses frequently cause the common cold, and thus absentees do not always have influenza (this issue was keenly pointed out by Minowa and others in this prefecture[5]). Thus, some suggest the use of fever as a criterion or methods for monitoring the change in HI antibody titers, and we agree with these suggestions. As we observed, however, inapparent infections accounted for approximately 20% of cases during epidemics, and these methods have a drawback; some aspects may be overlooked. Some researchers place emphasis on NI antibodies or NP antibodies.[6–8]

As described previously, we also used the absentee rate as a measure of epidemics to monitor epidemics in Maebashi City and emphasized the usefulness. We also used a similar method as many other researchers did and compared absentees between non-vaccinated and vaccinated areas to evaluate primarily the effect of the discontinuation of mass vaccinations on epidemics in elementary schools in Maebashi City. This also allowed us to examine absentees in vaccinated areas in comparison with Maebashi City, a non-vaccinated area, and evaluate the vaccine efficacy in a conventional manner.

First, in consideration of geographical conditions and annual epidemic size, Takasaki City, Kiryu City, and Isesaki City were selected for comparison from major cities in the prefecture. For reference, Annaka City was selected, which was a less populated city and provided no vaccinations like Maebashi City. As described previously, the size of the epidemic did not differ considerably among four cities (except Annaka City) in fiscal 1984 and 1985.

Second, we mentioned that the non-vaccinated group, which is often used in comparison with vaccinated areas, is statistically inappropriate. Instead, we used the absentee rate in Maebashi City, an overall non-vaccinated group, as a reference and calculated the vaccine efficacy rate in the two-dose group in vaccinated areas. The results showed low efficacy rates: 5% during the fiscal 1984 influenza B epidemic and 27% during the fiscal 1985 type A3 epidemic. However, these values were obtained on the assumption that all absentees were infected with influenza. The presence of persons who were infected but not absent (persons with inapparent infection) were important but not taken into consideration at this point.

However, some may want to know the efficacy in a situation where the ratio of vaccinated persons and non-vaccinated persons is 1:1 in the same area. In this situation, the qualitative difference between the two groups is very small.

In this situation, a study was recently conducted involving kindergartens, elementary schools, and junior high schools in Nara City during the fiscal 1984 influenza B epidemic.[9] With a sample size of 43,707 persons and a vaccination rate of 48.9%, the absentee rate and the proportion of persons with a temperature of 38°C or more were compared. The vaccine efficacy rate calculated from the reported data was 13.5% in absentees and 18.5% in persons with fever on the assumption that all absentees were infected with influenza. In the report, the authors expressed their impression that the efficacy was demonstrated but far from satisfactory as the values indicated. We agree completely.

With regard to this, we used our data to examine the vaccination rate, the overall absentee rate, and the absentee rate by the number of vaccine doses in all 11 cities in the Gunma prefecture (these are not referred to in the text). The results showed no significant correlation between the vaccination rate and the absentee rate. There was no correlation between the two-dose vaccination rate and the absentee rate at elementary schools, as shown in Figure 21.

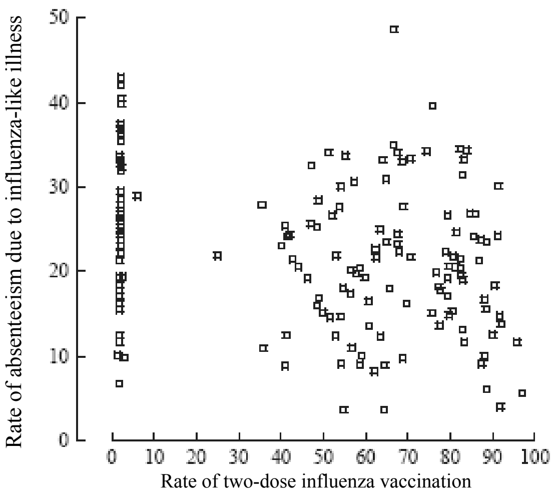


Figure 21. Correlation Between the Two-Dose Influenza Vaccination Rate and the Absentee Rate in Elementary Schools.

However, there was a correlation between the vaccination rate and the difference in the absentee rate between the non-vaccinated group and the two-dose group in the nine cities providing mass vaccinations during the fiscal 1984 influenza B epidemic (correlation coefficient, 0.80). Within the range of the vaccination rate of 40% to 90%, the regression equation was as follows: $y = 2.73 + 0.17x$. The estimate of the difference and standard error obtained from the equation at a vaccination rate of 50% was 11.23% ± 2.76%, and the value for Nara City fell within the range. The estimate at a vaccination rate of 85% was 17.18% ± 2.76%, and the value for Takasaki City fell within the range. This indicates that, in the case of influenza B, there is a modest correlation between the vaccination rate and the vaccine efficacy rate, and the relative efficacy rate may be estimated from the vaccination rate. However, when the equation is used with the mean absentee rate in the non-vaccinated group of vaccinated areas as a reference, an increase in the vaccination rate from 50% to 85% is associated with a modest increase in the vaccine efficacy rate from about 20% to 30%.

As pointed out previously, the conditional absentee rate we used and a simple absentee rate are only relative measures because not all absentees were patients with influenza and because some persons who were infected with influenza but attended classes were not taken into consideration. Thus, the vaccine efficacy rate calculated from these absentee rates is a relative measure. Even if some process is added on reasonable grounds to obtain a value as close as possible to the true vaccine efficacy rate, it is unlikely that the approximate efficacy rate is higher than expected.

Some may accept the notion that vaccines with a low efficacy rate in an epidemic population are useful in reducing symptoms in individuals. In this case, the proportion of infected persons in those attending classes could be higher in vaccinated areas than in non-vaccinated areas. Those children attend school and spread viruses, which may be responsible for increased absentee rates in non-vaccinated groups of vaccinated areas. In this regard, Sonoguchi demonstrated that schoolchildren who attend school and spread viruses contribute to school epidemics.[10]

Another issue to be addressed is the reason why the apparent vaccine efficacy rate was higher during the fiscal 1985 A3 epidemic than during the fiscal 1984 influenza B epidemic. One explanation is the lower efficacy of influenza B vaccine as generally acknowledged. Another explanation is that the fiscal 1985 A3 epidemic occurred earlier than usual. For example, the second dose of vaccine was administered during the epidemic period at about half the schools in Isesaki City and during the early stage of the epidemic at some schools in Takasaki City. At that time, some children were absent and many children had initial symptoms. These conditions probably increased the absentee rate eventually in the non-vaccinated group and the one-dose group.

Another issue is related to the one-dose group. Most surveys of this kind show that the absentee rate is often decreased in the following order: the non-vaccinated group, the one-dose group, and the two-dose group (not in all cases). This may make you think that, as the number of doses increases, the absentee rate decreases. However, the group should have a special condition that led to the discontinuation of vaccinations after the first dose. Some argue that a single dose of the vaccine is effective because of the booster effect. However, antibody titers in blood are expected to increase substantially only in persons with previous natural infection. However, there has been no study investigating the magnitude of the prophylactic efficacy against infection. If the efficacy is proven and it plays a significant role, vaccine efficacy should naturally depend on previous natural infection. If this is the case, the vaccine is effective only in persons who have been naturally infected with influenza sometime somewhere.

If vaccinees successfully avoid infection in a certain year, what will happen the next year? Most Japanese individuals older than 15 years rarely have an opportunity to receive vaccines. Are persons repeatedly vaccinated during school years better protected throughout adulthood? Does a vaccination provide protection at the individual level as well as the population level? We do not know the correct answers to these questions.

4) Influenza epidemics and HI antibody titers

Through investigations described in the preceding sections, we demonstrate that no particularly large epidemic occurred in Maebashi City after discontinuation of the mass vaccination of schoolchildren. In the investigation of the school absentee rate, we found no noteworthy difference in school epidemics. In a comparison of the absentee rate between vaccinated areas and non-vaccinated areas, we found that the vaccine efficacy rate was not as high as previously thought. We cast doubt on the significance of vaccinations in herd immunity even if vaccinations produce a certain efficacy rate.

Serological techniques should definitely be needed to address these questions. We have a responsibility to make utmost efforts to support the appropriateness of the discontinuation of vaccinations. As described in *Methods*, we conducted an unprecedented survey in Japan, which monitored HI antibody titers for five years in cooperation with approximately 600 elementary schoolchildren. The survey revealed that immunity acquired by natural infection with influenza was well maintained. Although the degree of herd immunity as assessed by HI antibody titer measurement decreased year after year, the rate of protection against the same type of viruses prevailing in the previous year, which was calculated by the formula for the vaccine efficacy rate, was high (about 80%, 70%, and 50% after one, two, and three years, respectively) even when epidemic virus strains continued to mutate. Thus, children had robust immunity against influenza. In addition, the degree of immunity is increased with repeated infections. More frequent previous infections were associated with lower infection rates and lower rates of disease onset after infection.

Next, about 60% to 70% of absentees during epidemics were infected with influenza, and those who were infected with influenza but attended classes (persons with inapparent infection) accounted for about 20% of the total. It was surprising that one in every five persons in class had inapparent infection, and those persons should have an important role in the spread of viruses.

We do not intend to perform field experiments for vaccine efficacy. It may be nonsense to make many speculations. Still, if mass vaccinations had not been provided, such conditions would have occurred in different regions during annual epidemics. We want to know what happens if vaccinations are provided in such a population.

Some may argue that vaccinations are justifiable if they demonstrate efficacy. As described in the preceding sections, however, the vaccine efficacy rate as assessed by the absentee rate was only 20% to 30%, which was smaller than the deviation of the annual infection rate among 600 study children in Maebashi City. No wonder the vaccine efficacy is not clearly apparent.

What justifies mass influenza vaccinations of schoolchildren under such circumstances? Without a convincing answer, Maebashi City will not resume vaccinations.

5) Summary and conclusion

(1) This report describes the background to the discontinuation of mass influenza vaccinations of schoolchildren in Maebashi City, history of close communication between the Maebashi Medical Association and the administrative body and engagement in vaccination programs, and the necessity for formation of the research group for the study of influenza.

(2) We showed influenza epidemic curves on the basis of the absentee rate in schools in the city, investigated the characteristics, and demonstrated that these curves provide better measures of epidemics than the number of closed classes that were commonly used as a measure of epidemics. We emphasized the usefulness of those curves as a means of observing influenza epidemics, which were easily feasible by summarizing absentee data routinely recorded by schools.

(3) The epidemic period was determined according to the criterion of 2% absentees, and the pattern of absentee curves was used to investigate the features of epidemics. These features were in good agreement with the features of epidemics assessed clinically and empirically.

(4) We had seven epidemics over a period of five years from January 1981 to December 1985. We compared the estimated number of absentees during each epidemic with data from the Report on the Notification of Patients with Influenza (including influenza-like illness) by the Gunma Medical Association and the Epidemic Control Information by the Ministry of Health and Welfare. The results showed that, after discontinuation of mass vaccinations, particularly abnormal influenza epidemics (in terms of the size of the epidemic and pattern) did not occur in elementary schools in Maebashi City. Macroscopically, epidemics in

Maebashi City simply occurred in parallel with those in the prefecture or in Japan.

(5) To evaluate how epidemics in Maebashi City were influenced by the discontinuation of the mass vaccination of schoolchildren in the city, we first selected non-vaccinated areas (Maebashi City and Annaka City/Usui-gun) and vaccinated areas (Takasaki City and six counties/cities) on the basis of the Report on the Notification of Patients with Influenza by the Gunma Medical Association (described above) and compared the number of patients per 100,000 population in each area to which each medical association belonged. There was no trend toward an increased number of patients in the non-vaccinated areas during each epidemic over a period of five years.

A similar method was used to investigate the National Health Insurance medical fees in non-vaccinated areas and vaccinated areas. We calculated the ratio of the number of clinical visits, total medical fee points, or medical fee points per visit from December to February (including an epidemic period) relative to the corresponding value from September to November (before influenza epidemics). There was no significant change in medical fees between the pre-epidemic period and the epidemic period. No differences were found between non-vaccinated areas and vaccinated areas.

In addition, the 10-year mean mortality curves were drawn for Maebashi City, Gunma Prefecture, and Takasaki City, and actual mortality rates were compared before and after discontinuation of vaccinations in Maebashi City. There was no evidence that the mortality rate after discontinuation of vaccinations was high, particularly during influenza epidemic periods in Maebashi City. These findings suggest that excess mortality was unlikely to be increased.

Taken together, we concluded that discontinuation of mass vaccinations in Maebashi City was not associated with more patients with influenza, higher health care costs, or higher mortality rates in older individuals or high-risk individuals compared with other areas.

(6) In a report on the absentee survey involving all high schools, junior high schools, and elementary schools in the prefecture during the fiscal 1984 influenza B epidemic and the fiscal 1985 A/H_3N_2 epidemic, we selected Maebashi City (non-vaccinated area) and Takasaki City, Kiryu City, and Isesaki City (vaccinated areas) and compared the absentees at municipal elementary schools. After finding no substantial difference in the absentee rate between the three cities and Maebashi City, we calculated the vaccine efficacy rate in the two-dose group of the three cities while using the absentee rate in Maebashi City as a reference control. The results showed that the rate was 5.1% during the influenza B epidemic and 26.7% during the A/H_3N_2 epidemic. We also investigated the conditions in Takasaki City, which was located next to Maebashi City and had a similar population and epidemic size. During the influenza B epidemic, the total absentee rate was 42.8% in Maebashi City and 40.1% (−2.7%) in Takasaki City. The absentee rate was 38.3% in the two-dose group (vaccination rate, 85.6%) of Takasaki City. Thus, the vaccine efficacy rate was 10.5%. During the A/H_3N_2 epidemic, the total absentee rate was 27.7% in Maebashi City and 21.0% (−6.7%) in Takasaki City. The absentee rate was 18.6% in the two-dose group (vaccination rate, 80.5%). Thus, the vaccine efficacy rate was 32.9%.

The vaccine efficacy rate calculated from the absentee rate was not more than about 30% in the group with a vaccination rate higher than 80%. When regional differences in the size of the epidemic were taken into consideration, there was no correlation between the vaccination rate and the absentee rate in elementary schools in different cities of the prefecture.

(7) We measured HI antibody titers in the same population of approximately 600 children with no previous vaccination at five elementary schools in Maebashi City for five years. The measurement was started when they were second graders in 1986 and continued until they became sixth graders. Tests were performed in November and May during which an annual epidemic occurred. During our survey period, six epidemics occurred: (1) B from January to February 1982, (2) A/H_3N_2 from February to March 1982, (3) A/H_3N_2 from January to February 1983, (4) A/H_1N_1 from December 1983 to February 1984, (5) B from January to February 1985, and (6) A/H_3N_2 from November to December 1985. Among these, epidemics

1, 3, 5, and 6 were of middle scale or greater and associated with an infection rate of 40% to 50% as assessed by HI antibody titer measurement. The absentee rate during each epidemic period was 40% to 50%, and the infection rate among absentees was 60% to 70%.

Persons who were infected but not absent from school (persons with inapparent infection) accounted for approximately 20% across all epidemics; one in every five enrolled children had inapparent infection. Attention should be paid to the role of these children in the spread of viruses.

(8) By looking through the entire epidemics, infection rarely occurred in persons with an HI antibody titer of 128-fold or more. As the antibody titer decreased, the infection rate increased. The infection rate was 60% to 80% in persons with a titer less than 16-fold.

(9) Analysis of the temporal change in the distribution of HI antibody titers showed that immunity acquired by influenza infection was well maintained. In the examination of influenza B, it was estimated that it took about three years for the distribution of antibody titers in the infected group to return to a pre-infection pattern.

(10) The effect of previous infection was investigated during each epidemic period. More frequent previous infections were associated with lower infection rates and lower rates of disease onset after infection. In general, the ratio of the infection rate in persons who were not infected during a previous epidemic period relative to that in persons who were infected was 2:1. Although the degree of immunity in the population in terms of HI antibody titers decreased year by year, the rate of protection against the same type of virus, which was calculated by the formula for the vaccine efficacy rate, was high (about 80%, 70%, and 50% after one, two, and three years, respectively). Thus, children acquired robust immunity when naturally infected with influenza.

(11) These analyses did not provide justification for resuming mass influenza vaccination of schoolchildren in Maebashi City.

III. Our Opinion on Mass Influenza Vaccination

Vaccinations provide two benefits. One is protection of vaccinees against infection, and the other is prevention of epidemics in the population. As described repeatedly, we are interested in the usefulness of compulsory mass vaccinations of children and students. Thus, our main theme is to investigate the efficacy in preventing epidemics. However, substantially potent efficacy in protecting individuals against infection (polio, for example) may directly lead to prevention of epidemics, and the two types of protection are not totally independent. Unfortunately, the protective efficacy of the influenza vaccine against infection is insufficient, and influenza is an epidemic with characteristics different from those of other viral diseases. Thus, the protective efficacy against infection should be distinguished from the efficacy in prevention of epidemics when the usefulness of the vaccine is discussed. With the circumstances in mind, we form our opinion on mass influenza vaccinations.

1. Peculiarities of influenza

Influenza is different from measles and varicella in the following points.

a) Influenza repeats explosive epidemics annually.
b) Influenza causes lesions limited to the upper airway mucosa but rarely induces viremia. The incubation period is therefore short.
c) The virus mutates substantially.
d) Immunity is incomplete and short-lived.

Because of these features, influenza-specific measures are required to prevent influenza epidemics. Influenza causes explosive epidemics repeatedly because of strong infectivity of the virus and the presence of many sensitive individuals. Immunity acquired by infection is incomplete and short-lived probably because infection with viruses is limited to the upper airway mucosa and does not cause viremia. Thus, persons with a history of infection remain susceptible to the disease. To prevent infection by vaccination, vaccine doses for the whole population are needed. Moreover, viruses mutate, and different vaccines have to be manufactured every year. Under the circumstances, Sabin argued that it is not practical to use inactivated vaccine for the prevention of epidemics.[11,12]

In Japan, schools are considered incubators for the growth of influenza viruses, and schoolchildren and students are vaccinated for the protection of the entire community. As described previously, this strategy is based on a few assumptions. However, people had to rely on this strategy for the prevention of influenza epidemics probably because of the peculiarities of influenza disease.

2. Fate of inactivated influenza vaccine

Because influenza infects the upper airway mucosa, it is difficult to prevent infection with blood antibodies. IgA and cell immunity are believed to play an important role in the prevention of infection in the superficial layer of the mucosa. Inactivated vaccine does not induce IgA production.[13] Reiss et al. ruled out the induction of cell immunity,[14] whereas Yamada et al. showed the possibility of induction.[15] Stuart-Harris reported that inactivated vaccine induces only a modest immune response in persons without antibodies before vaccination and that natural infection confers more extensive immunity than inactivated vaccines and allows for some mutation.[16] He emphasized the need for live vaccines.

If vaccine-induced IgG antibodies in blood prevent severe forms of influenza but do not suppress the growth of viruses in the upper airway mucosa, the vaccine is not useful in preventing epidemics because schoolchildren continue to discharge viruses. Given that infection immunity is incomplete but sustainable, IgA antibodies with a short half-life are not the only mechanism for the protection against infection. It remains to be proven whether an inactivated vaccine suppresses the growth of viruses in the mucosa, and the grounds for using this vaccine for the prevention of epidemics are lacking.

Viral mutations are another problem. It is very difficult for an inactivated vaccine to suppress such a frequently mutating virus. During recent epidemics, an antigenic match was rarely achieved.

Antigenically mismatched vaccines are less effective or not effective at all, and this is a tragedy. Some point out that the influenza vaccine serves merely a booster and does not immunize individuals. Although the original antigenic sin is widely known, Yamane et al. reported that the antibody titer substantially increased after vaccinations in children infected with a USSR strain from 1977 to 1978 but poorly increased in children not infected and that vaccines may have a booster effect but not prime children.[17] Odagiri et al. reported similar results in 1979.[18] Fuse et al. statistically analyzed the results at junior high schools in Agatsuma-gun in this prefecture and reported that the mean increase in HI antibody titers after vaccination was about 2-fold.[19] This may be attributed to previous infection. These factors should limit the efficacy of an inactivated vaccine. In particular, vaccine that cannot prime immunity does not provide protection against viruses with antigenic shift.

3. Protection against infection by influenza vaccine

As described previously, a vaccine with a potent protective efficacy against infection should prevent epidemics. As a part of an examination of the policy of mass vaccinations, we wanted to know the protective efficacy of current vaccines against infection. A vaccine with an antigenic match is believed to have an efficacy rate of 80%.[20] The figure is not achieved in actual situations because antigenic matches are uncommon. In addition, the results of many study reports published yearly have substantial variability, which complicates the evaluation. This is also associated with the elusive nature of influenza disease, and a couple of related problems are reviewed.

1) Morbidity or infection

The efficacy of a vaccine in morbidity is quite different from the efficacy in infection. Morbidity surveys are common, but it is difficult to exclude the common cold in such surveys.

Infection surveys on the basis of antibody levels are accurate but have some problems. One of those problems is the selection of an indicator. HI antibodies are usually measured. Some pointed out that the antibody titer did not increase with infection in a group of persons with high antibody titers, leading to overestimation of the vaccine efficacy.

In a survey by Honma et al.,[7] the vaccine efficacy rate calculated from HI antibodies was 44.2% but did not reflect the actual conditions. They reported that the rate calculated from NP antibodies (15.8%) better reflected the conditions.

Another problem is inapparent infection. Our survey showed that asymptomatic persons with an increase in antibody titer accounted for about 20% during each epidemic period. Interpretation of these persons has a considerable effect on the survey results. Influenza is not diagnosed in asymptomatic persons with infection. From the viewpoint of personal protection, persons with inapparent infection should be considered protected. However, these persons may discharge viruses and cannot be ignored from the viewpoint of epidemic prevention. (We isolated viruses from asymptomatic persons.)

In contrast, for the investigation of incidence, absentee surveys are often conducted. Procedures for excluding other common cold-like diseases are important in these surveys. Fever is commonly used as a criterion. Minowa et al. considered a temperature of 38°C or more a sign of influenza,[5] and Honma et al. reported that a temperature of 37°C or more was a practical measure of influenza.[21] Whichever criterion is used, these methods may help identify persons probably infected with influenza among absentees. Still, uncertainty of a questionnaire used in a symptom survey is a problem. In addition, persons with mild conditions such as those with inapparent infection may be overlooked. Thus, all numerical variables are only a relative measure. Efforts should be made to clarify the truth while taking those limitations into consideration.

We used the absentee rate as a measure of school epidemics and supported the data by asking parents to document symptoms in an absentee form and submit it whenever children were absent. In addition, HI antibodies were measured as an infection survey. Our survey was not perfect; however, we believe that our study fairly accurately elucidated the actual conditions of epidemics.

2) Problem with grouping in a school-based survey

When vaccine efficacy is investigated in schools, children are usually divided into the following groups for observation: persons vaccinated twice, persons vaccinated once, and non-vaccinated persons. Under a condition of statutory vaccinations, such grouping cannot be performed in a planned manner. Persons are grouped incidentally. Thus, the non-vaccinated group consists of persons with a disease, those with a contraindication to the vaccination, those absent on the day, and those refusing to receive the vaccine. The group should be considered a population with characteristics different from those of the whole population of vaccinees. You may make an error in judgment when disregarding the difference between populations.

In a study by Shibata et al.,[22] for example, the incidence of influenza was 24.6% in persons receiving two doses of the vaccine and 40.0% in non-vaccinated persons, and the vaccine efficacy rate was 38.5%. The incidence of the common cold with fever (not related to influenza), which was simultaneously surveyed, was 51.0% in persons receiving two doses and 73.3% in non-vaccinated persons. This means that the efficacy rate of the vaccine in preventing the influenza-unrelated common cold with fever was 30.4%. This may be attributed to the imbalance between the two populations.

As we show in Figure 8, it is obvious when the non-vaccinated population in all schools is used for reference. The incidence of influenza was higher in the non-vaccinated group of vaccination schools than in non-vaccinated schools, and the mean incidence in all vaccination schools was similar to that in non-vaccinated schools (see II-3-C). Results should be evaluated while taking into consideration that the non-vaccinated group is a population with more days missed from school and a higher risk of fever (unrelated to vaccine efficacy).

Despite this, the efficacy rate in schools is not high. Minowa et al. reported a rate of 44.4%.[23] Shibata et al. reported that the rate was 38.5% in 1981, 4.7% in 1982, 73% in 1983, and 26.7% in 1984.[24] Yamanaka et al. reported a rate of 11.9%.[25] Oda et al. reported a rate of 0%.[26] Oda et al. reported a rate of 11%.[27] Ohga et al. reported a rate of 10.0%.[28] Matsubara et al. found no difference in the incidence between persons receiving two doses of the vaccine and non-vaccinated persons during the 1985 influenza B epidemic.[29] Yamamoto et al. found no evidence that the vaccinated group had less incidence or milder symptoms during the 1977-1978 epidemic.[30] Fuse statistically investigated the results at three junior high schools and concluded that there were some significant differences between vaccinated and non-vaccinated groups but there was no significant difference overall.[31]

In general, vaccines with an efficacy rate of 70% are put to practical use. The efficacy rate of the influenza vaccine in schools is much lower than the value. The rate differs considerably depending on the fiscal year and area. It may be understandable because influenza and the common cold are constantly changing epidemic diseases. In other words, vaccine efficacy is not potent enough to modify epidemics. Even when statistically significant efficacy is found, the efficacy may be offset by annual fluctuations and geographical differences.

Some argue that high vaccination rates may make up for low efficacy rates. However, Sakurada et al. reported an infection rate of 69.5% in a population with a high vaccination rate of 92.8% in a survey in 1978.[32] Matsubara et al. conducted a survey in 1983 and found no considerable difference in the mean incidence between 45 schools with a vaccination rate of 80% (24.7%) and 11 schools with a rate of 60% or less (31.4%).[29]

We investigated the relationship between the vaccination rate and the absentee rate in elementary schools in Gunma Prefecture and found no evidence that higher vaccination rates were associated with lower absentee rates. Teachers and school physicians engaged in school health have been making efforts to increase the vaccination rate. They were frustrated by the failure to prevent epidemics despite their efforts. We hope the Ministry of Health and Welfare will take scientific action instead of using a hollow theory to disregard their feelings.

3) Need for long-term surveys

The features of influenza vary year by year. Moreover, previous infections may modify epidemics, and thus it is difficult to elucidate the true nature by a single-year survey.

Hoskins et al. vaccinated and followed up the same group of children for seven years.[33] The vaccine was effective during the first year of vaccinations, but the efficacy was not evident during subsequent epidemics because the first vaccine suppressed the efficacy of subsequent vaccines against mutant strains. Throughout the entire follow-up period, there was no difference in the incidence between the vaccinated group and the non-vaccinated group. They reached the following conclusions. Children who acquire immunity through natural infection are protected even during a period of antigenic drift. When a new type emerges, administration of the vaccine against it is effective, but the efficacy is short-lived. Vaccine against the subsequent mutant strain is not effective, and persons are eventually infected. Annual vaccination of children confers no long-term advantage.

Sonoguchi et al. pointed out that the problem was in the design of the survey, that is, an incidence survey.[34] They argued that infection immunity should not be maintained for such a long time if assessed in terms of the infection rate. However, we measured HI antibody titers in the same children for five years and demonstrated that natural infection-induced immunity was well maintained (see II-3-D).

Smith et al. followed up post office employees for five years.[35,36] They selected vaccinated offices and unvaccinated offices and conducted a survey on sick leave. The results showed that the absentee rate was lower in the vaccinated group and that the vaccine was considered cost-effective. However, the absentee rate was also lower outside the influenza epidemic period, suggesting that the rate reduction may result from increased awareness of health and influenza after vaccinations (placebo effect). They argued that the influenza vaccine produced good results but had a weak preventive effect on influenza and that adverse reactions, such as Guillain-Barre syndrome, although infrequent, should be taken into consideration. They stated that workers who were informed of possible adverse reactions would not receive the vaccine (even if those reactions did not medically offset vaccine efficacy).

Such a follow-up survey is very important in determining the practical value of the vaccines. Influenza is modified by previous epidemics,[37] weather conditions,[38] lifestyle,[39] and social conditions, and its features change year after year. Results of single-year surveys are misleading; the vaccine may be effective in a certain year and ineffective in the following year.

This is why we followed up the same schoolchildren for five years. The survey allowed us to demonstrate that discontinuation of vaccinations did not result in large epidemics and that infection immunity was well maintained.

4. Role of infection immunity

Infection immunity for influenza is believed to be weaker than that for other viral diseases. However, in 1977, an outbreak caused by H_1N_1 strain occurred 20 years after the previous one, among persons 20 years of age or younger, but did not in persons 20 years of age or older who had antibodies against the strain. This suggests that infection immunity, although weak, is maintained and strongly modifies epidemics. Immunity acquired by natural infection is known to work even at the time of minor mutations. Influenza viruses repeatedly undergo antigenic drift and antigenic shift (about once a decade) to evade infection immunity in humans rather than vaccine-induced immunity. All people may be infected a few times over a period of 10 years and acquire a certain level of immunity that prevents the occurrence of epidemics.

In the five-year follow-up survey, we demonstrated that previous infection provided effective protection against infection with the same type of virus (with substantial antigenic mutations). We found that repeated infections were associated with greater protection (see II-3-D).

The results reported by Hoskins suggest that protection against infection may depend on previous infection and that modification by vaccination may only be transient.[33] Oyama et al. reported similar findings that the 1979 H_1N_1 epidemic was limited to persons 25 years of age or younger in an area not affected by the previous epidemic, regardless of vaccination.[41]

An epidemic is small when the virus type is the same as that in the previous year. On this occasion, antigens of the vaccine strain are matched to those of the epidemic strain, but this does not mean that the vaccine suppresses the epidemic. This should be taken into consideration when vaccine efficacy is discussed.

Infected children acquire immunity and become resistant to the same type of virus (and they will not be infected or asymptomatic despite infection). The process is probably unrelated to the presence or absence of vaccinations. We therefore believe that schoolchildren do not benefit from vaccinations.

5. Protection of the community by influenza vaccine

Although the incidence of influenza is high in schoolchildren, influenza causes serious conditions only in preschool children and older individuals.[42] The Japanese strategy involving vaccinations of healthy schoolchildren aims to suppress epidemics in schools, prevent the spread of influenza in the community, and thereby protect high-risk groups. Does the strategy work? This is our chief concern. Because compulsory mass vaccinations of schoolchildren are provided according to the strategy, studies should be conducted to justify the strategy. Unfortunately, no study data are available in Japan.

In 1979, a research group in the United States came to Japan to investigate in detail the Japanese vaccination policy and epidemics.[43] The group reached the following conclusion: (1) The effect of the Japanese vaccination program on the transmission of influenza, morbidity, and mortality is not clear. (2) It is difficult to predict a positive impact from a program like Japan, if feasible.

Monto et al. administered vaccine against a Hong Kong variant of influenza A to schoolchildren in Tecumseh City, Michigan, (population, 7500) and investigated respiratory disease in citizens during the subsequent A/Hong Kong epidemic.[44] The results showed that the rate of increase in respiratory disease was one-third that in Adrian City, an adjacent city. However, there was no difference between the two cities during an influenza B epidemic occurring two months later.

It is ironic that the Japanese policy is not validated in Japan but in the United States. The study by Monto et al. was well designed and should be evaluated highly. However, a few problems arise when their results are extrapolated to Japanese conditions. First, their experiment was performed during the 1968–1969 winter epidemic immediately after the appearance of the Hong Kong strain, and they were able to predict the epidemic virus. A complete match of strains was achieved. That was an experiment on the basis of a rare opportunity, and the scenario does not reflect annual vaccinations against an annual epidemic. Moreover, they reported results during the first year of vaccinations, and their long-term outcomes may end up something similar to the results reported by Hoskins.

Second, their experiment was performed in a rural village. It should be noted that the conditions are quite different from those in Japan, a densely populated, heavily trafficked country. In Japan, influenza sweeps across the country. It is obvious that this cannot be explained by the spread by schoolchildren.

In a survey of households of infected children in Kumamoto Prefecture during a Hong Kong influenza epidemic in 1976, Sonoguchi et al. found that the disease developed earlier in 28 of 105 persons (27%) than in schoolchildren.[44] Viruses were isolated. These findings made them draw the following conclusions. Persons spending time in an epidemic region during the New Year's holidays came back home with viruses, which probably spread to family members and caused a latent epidemic widely throughout the prefecture. Shortly after schools were opened after winter holidays, multiple schoolchildren infected at home served as a source of infection and spread viruses at their school, leading to outbreaks in the school. Similar incidents everywhere in the prefecture resulted in multiple outbreaks in a short period of time. Director Sonoguchi stated that no such process was found in his years of experience, but this may reflect recent social circumstances in Japan.

At any rate, it is uncertain whether high-risk groups can be protected by mass vaccinations of schoolchildren with inactivated influenza vaccine. Some mention the efficacy of the vaccine in reducing symptoms to justify mass vaccinations, but this is a mere quibble.

The contention about mass influenza vaccinations is not related to infection or morbidity. The point is whether vaccinated children stop discharging viruses or not. At present, no clear answer is available. Oyama et al. isolated the 1978 H_3N_2 virus from 9 of 22 persons in the vaccinated group and 11 of 22 non-vaccinated persons.[41] Sugaya et al. surveyed the 1983 H_3N_2 epidemic in schoolchildren and preschool children and isolated the virus from 8 schoolchildren and 11 preschool children.[46] Of these, 3 schoolchildren and 2 preschool children were vaccinees.

These findings suggest that the effects, such as protection against infection and prevention of morbidity, should be distinguished from the epidemic-preventive efficacy. The policy of vaccination of schoolchildren for protection of high-risk groups appears to be based on a philosophical principle, and scientific evidence is lacking.

We conducted a survey for five years after discontinuation of mass vaccinations and found no evidence of greater epidemics with respect to all measures of the number of patients with influenza, health care costs during epidemic periods, excess mortality, and the incidence in schoolchildren after discontinuation of vaccinations in Maebashi City. Examination of school absentee curves showed that a larger nationwide epidemic was associated with a larger epidemic in Maebashi City and that an earlier than usual onset of a nationwide epidemic was associated with the earlier onset in Maebashi. The scale, pattern, and period of epidemics were similar in Maebashi and the country as a whole (see II-3-A). Our survey results, although obtained by observation of small areas, suggest that discontinuation of vaccinations appears to lead to no substantial changes. The preconceived idea of being protected by vaccinations should be discarded, and the function of the vaccine to protect communities should be assessed.

6. Vaccination of high-risk groups

The vaccination of healthy schoolchildren is a policy adopted only in Japan. Foreign countries recommend the vaccination of high-risk groups only. Many believe that Japan should also adopt that approach. For example, Mizutani argued that it seemed to be very difficult to protect the community with such vaccines.[44] He also stated that, although it is difficult for currently available vaccines to completely prevent infection, those vaccines appear to be effective in reducing symptoms during infection and should be administered to high-risk individuals and persons who are annoyed by even transient infection with influenza. Kitayama argued that it is difficult to determine whether mass vaccinations of schoolchildren are effective in reducing influenza epidemics and that there has been no clear answer to the question.[47] He concluded that it depends on epidemics whether the incidence is highest in schoolchildren and whether schoolchildren are infected first and play a role as an amplifier of epidemics. He added that there is no accurate, specific data on the prevention of epidemics in the actual community or the decrease in the morbidity and excess mortality. During a round-table discussion, Mikio Kimura said that a method for protection of susceptible persons should be considered in Japan. In response, Munehiro Hirayama said that he administered the vaccine to his father but not himself or his children.[48]

In an immunological analysis of influenza-related mortality in older individuals, Takahashi et al. reported that deaths of young individuals from influenza markedly decreased but deaths of individuals 65 years of age or older increased and argued that older individuals should be vaccinated against influenza.[49] They vaccinated older individuals and found elevated HI antibody titers in about half of those individuals.[50] There are also reports on the vaccination of patients with underlying diseases[51] and those undergoing hemodialysis.[52]

If the influenza vaccine is less likely to prevent epidemics but is likely to reduce symptoms, you may recommend the vaccination of older individuals and patients after discontinuation of compulsory vaccinations of schoolchildren. In this case, insufficient potency of the vaccine is a concern.

In the above-mentioned report by the US research group,[43] they reported that the vaccination of high-risk groups is recommended in the United States. They stated, however, that the recommendation is based on the protective efficacy demonstrated in a short-term observation and that there is no evidence that annual vaccinations reduce influenza-associated mortality. They added that, at any rate, careful, long-term studies are required. Mizutani pointed out that, from the medical point of view, the vaccine should be indicated for persons who are likely to have severe disease when infected with influenza (older individuals, children, and patients with tuberculosis, bronchial asthma, or diabetes mellitus).[53] He cautioned, however, that these persons are particularly sensitive to adverse reactions and that the vaccine should be administered with care despite a marked reduction in adverse reactions after practical application of the HA vaccine. His argument is worth listening to.

7. Adverse reaction to influenza vaccine

We did not survey adverse reactions to the influenza vaccine. Yugami, a group member, investigated cases of adverse reactions to vaccines reported in original papers in Igaku-Chuo Zasshi before 1970 and identified a total of 11 patients with reactions to influenza vaccines, including three with encephalitis, three with acute optic neuritis, one with central retinitis, one with transverse myelitis, one with ophthalmopathy, and two deaths due to shock.[54,55] Of these, the patient with ophthalmopathy had uveitis together with macular atrophy.[56] The three patients with optic neuritis were reported by Yutaka Aoki, a former president of the Maebashi Medical Association.[57] These reports suggest that adverse reactions to influenza vaccine may occur predominantly in the nervous system. Then, we were shocked by multiple cases of Guillain-Barre syndrome reported after swine influenza vaccinations in the United States in 1976.[58]

In Japan, adverse reactions have been rare since the use of the HA vaccine in 1972. Still, those patients accounted for 26% of certified patients with vaccine-related health hazards, and the influenza vaccine is the most common cause of those reactions.[59] Kakuta estimated that adverse reactions requiring hospitalization occur once every 25,000 injections.[60] Given this proportion and a vaccination rate of 80%, about three persons may experience such reactions annually in Maebashi City with a population of 270,000, which are not negligibly small. These reactions may possibly include serious neuropahy.[61–63]

8. Conclusions

Many questions are raised about the unique Japanese policy of compulsory mass vaccinations of healthy schoolchildren for protection of the community against influenza. It is not advisable to stick to the conventional practice without clear grounds. It is time to switch from community protection to personal protection or from mass vaccinations to individual vaccinations. Nevertheless, the efficacy of currently available vaccines is far from satisfactory. At any rate, we hope that more effective vaccines will be developed according to strategies devised on the basis of sufficient studies.

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V. Appendices

[Appendix 1] Efficacy of mass influenza vaccination Study of epidemics in Maebashi City in 1977

Shuzo Yugami, Shigeo Kuwashima, and Hideaki Yagi (Members of Maebashi Medical Association, practitioners)

Introduction

A large, nationwide influenza epidemic occurred from January to March 1977, with an estimated number of patients exceeding 2.4 million. The epidemic was caused primarily by influenza B virus. Influenza B virus is believed to be less likely to cause explosive epidemics; however, the size of the epidemic was larger than that of the influenza A epidemic in the previous year.

As a means of preventing influenza epidemics, mass vaccinations were provided in junior high schools, elementary schools, childcare centers, and kindergartens in Japan. Why do large epidemics occur despite annual vaccinations? We wonder whether vaccines really work well. As annual vaccinations cannot prevent epidemics, we may as well discontinue vaccinations. Would greater epidemics occur after discontinuation? Such simple doubts led to this survey.

When the vaccination status in Maebashi City was surveyed, mass vaccinations were provided in all elementary and junior high schools but was not at about half the childcare centers and kindergartens. This allowed us to compare vaccinated facilities with non-vaccinated ones and to conduct the following survey.

Survey results

1. Epidemic conditions

The number of classes closed at elementary schools in Maebashi City is graphically presented in Figure 1. This shows an epidemic from the end of January to the end of February.

2. Influenza vaccination rate and the number of absentees (elementary schools)

Mass vaccinations were provided in all elementary schools, but the vaccination rate varied from 57% to 100%. The ratio of the total number of absentees to the number of enrolled children was used as a measure of the incidence, and the correlation between the measure and the vaccination rate was investigated. As shown in Figure 2, there was no correlation between the two variables. There was no evidence that higher vaccination rates were associated with lower numbers of absentees.

3. Epidemic period and the vaccination rate at elementary schools

Among elementary schools in the city, those with 700 students or more were selected and listed in ascending order of the influenza vaccination rate. A single horizontal line indicates each class closure (Figure 3). The epidemic began at the Ootone Elementary School. This is often the case with pediatric epidemic diseases in Maebashi City, which may be explained by geographical conditions. Ootone Residential Complex is located in the southwest area of Maebashi City and has a heavy flow of traffic to and from Takasaki City, Saitama Prefectures, and Tokyo.

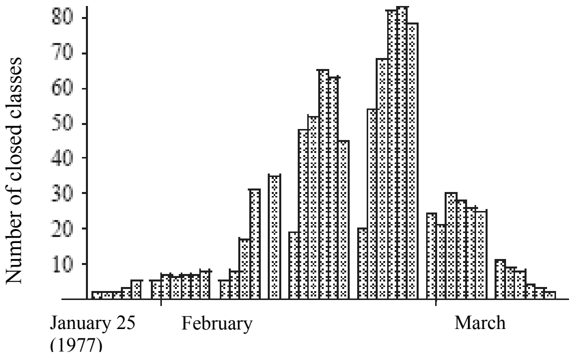

Figure 1. Class Closure Caused by Influenza (Elementary Schools).

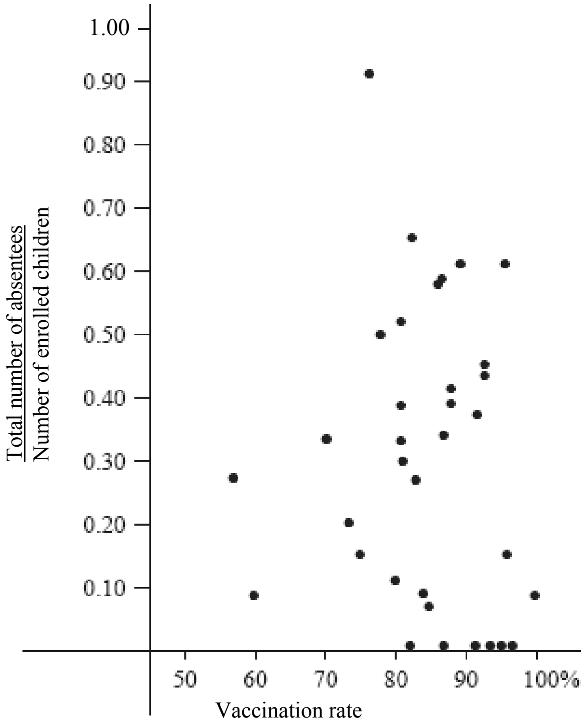

Figure 2. Correlation between the Influenza Vaccination Rate and the Measure of Incidence (Elementary Schools).

Elementary school	Vaccination rate
Eimei	57
Shikishima	60
Amagawa	75
Ootone	77
Motosouja	78
Hirose	81
Nakagawa	81
Asakura	82
Iwagami	83
Momonoi	83
Kaigaya	84
Jonan	87
Momokawa	87
Hosoi	88
Momonose	91
Joto	92
Wakamiya	96

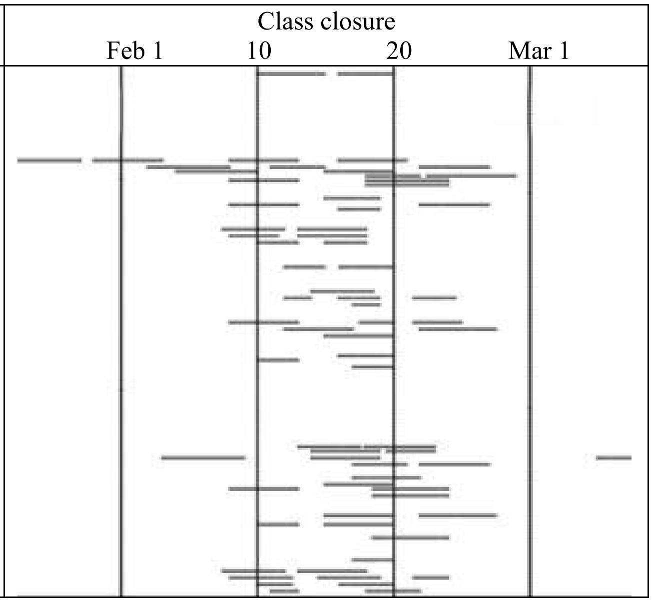

Figure 3. Class Closure and Vaccination Rates (Elementary Schools).

Figure 4. Order of Epidemics in Elementary Schools in the City.

Other elementary schools simultaneously closed classes around February 10. Class closure did not occur at Shikishima Elementary School with a vaccination rate of 60%, Amagawa Elementary School with a rate of 75%, Kaigaya Elementary School with a rate of 84%, and Jonan Elementary School with a rate of 87%. This suggests that elementary schools with low vaccination rates were unlikely to play a leading role in the spread of epidemics.

4. Geographic route of epidemics

On the map, elementary schools in Maebashi City are plotted together with numerals indicating the order of the start of class closures. Class closures occurred first at Ootone, followed by Souja, Ninomiya, and Fuzoku; however, class closures occurred almost simultaneously, and the epidemic route was not identifiable. Elementary schools with low vaccination rates and no class closures, such as Shikishima Elementary School and Amagawa Elementary School, were not isolated geographically. (Figure 4).

5. Incidence at childcare centers and kindergartens

Among childcare centers and kindergartens in Maebashi City, mass vaccinations were not provided at 14 private facilities. Mass vaccinations were provided at all municipal facilities, although the vaccination rate varied from 30% to 80%. There was no correlation between the vaccination rate and the incidence among municipal facilities (Figure 5).

6. Absentee rate at facilities without mass vaccination

It was difficult to determine the accurate incidence at private facilities. Thus, the number of absentees on February 14 (peak) was surveyed and compared. Again, there was no difference between facilities with mass vaccinations and those without (Figure 6).

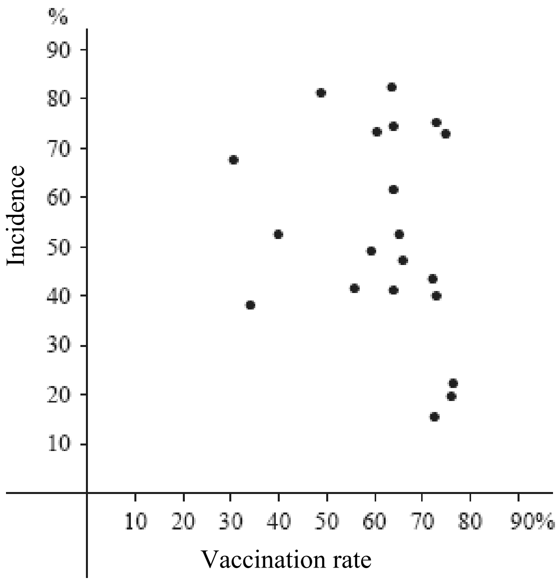

Figure 5. Incidence in Preschool Children at Childcare Centers in February 1977.

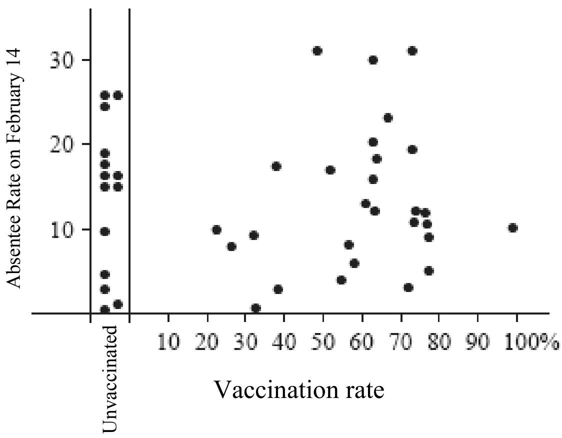

Figure 6. Influenza Vaccination Rate and Absentee Rate at Childcare Centers.

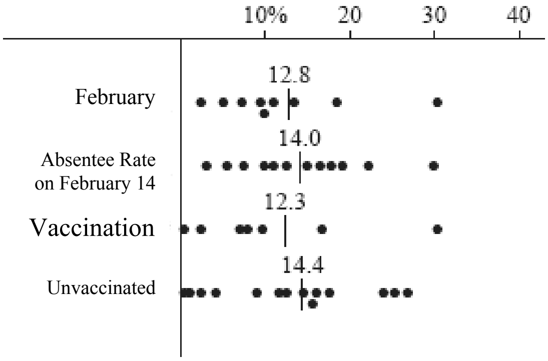

Figure 7. Absentee Rate on February 14.

For comparison, these facilities were divided into the following four groups: facilities with a vaccination rate of 70% or more, those with a rate of 50% or more, those with a rate less than 50%, and those without vaccination (Figure 7). The mean rate of absentees was 12.8% in the 70% group, 14.0% in the group with a rate of 50% or more, 12.3% in the group with a rate less than 50%, and 14.4% in the group without vaccinations. There was no difference among the four groups.

Discussion

Although this study was not a prospective one and had some limitations, the following findings were obtained on influenza epidemics in Maebashi City during the year. (1) The influenza vaccination rate did not influence influenza epidemics in elementary schools. Elementary schools with low vaccination rates were unlikely to play a leading role in the spread of epidemics. (2) The degree of epidemics did not differ between childcare centers and kindergartens with mass influenza vaccinations and those without.

In Japan, mass influenza vaccinations of healthy children are now provided at childcare centers, kindergartens, elementary schools, and junior high schools. Japan is the only country to take this approach. In Europe and the United States, high-risk children and older individuals are selectively vaccinated.[1–3] In Japan, mass vaccinations are provided because schools are considered amplifiers of influenza epidemics and because prevention of school epidemics is believed to indirectly prevent infection of high-risk children and older individuals. In other words, healthy children are vaccinated for the benefit of the protection of high-risk children and older individuals.[4] Ebisawa strongly objected to the policy,[1] stating that mass vaccinations of healthy children should be discontinued because healthy children, if infected with influenza, do not have a severe disease. In addition, he stressed that the fundamental difference in opinions between Japanese researchers and those in Europe and the United States lies in the difference in the value of human lives.

We agree with Ebisawa. The Japanese policy of mass vaccinations should be based on the ability of the influenza vaccine to prevent epidemics. It is obvious that the ability to prevent the onset of disease is needed to prevent epidemics. Ebisawa presented literature inside and outside Japan and denied that the influenza vaccine is effective in preventing the onset of disease.[5] Hirayama argued that the influenza vaccine is less likely to produce the expected efficacy because influenza disease is caused by viruses with antigen structures that are slightly different from those in the previous epidemic and because antigenic viruses growing in cells on the surface of the throat are not readily influenced directly by blood antibodies.[6] Sano argued that inactivated influenza vaccine is effective but not very effective.[7]

The influenza vaccine induces the production of serum antibodies but not antibodies in airway secretions.[8,9] After infection with influenza, however, virus-neutralizing IgA antibodies appear in airway secretions, which provide protection against infection.[10,11] Kawakami reported that many viruses infecting the respiratory tract, such as influenza viruses, grow in the respiratory mucosa and cause diseases after a short incubation period without inducing viremia.[12] He also argued it cannot be helped that viruses entering and growing in the respiratory mucosa are not strongly suppressed by blood antibodies and eventually cause more or less symptoms even if blood antibody levels are elevated by the inactivated influenza vaccine and if vaccine strains are antigenically matched to epidemic strains.

Oda recently investigated in detail the epidemics at Tsumagoimura Elementary School and reported in the Gunma Prefectural Medical Bulletin that there was no difference in the incidence between vaccinated children and unvaccinated children.[13] Oda's study investigated the association between the vaccination status and the incidence in individual children, whereas we investigated the association between the vaccination status and epidemics at facilities. Oda's report together with our results suggests that vaccinations appeared to be ineffective in preventing the onset of disease and epidemic during the 1977 influenza epidemic.

Mass vaccinations of healthy children in childcare centers, kindergartens, elementary schools, and junior high schools are nonsense if the influenza vaccine does not have the ability to prevent the onset of disease and epidemics.

The influenza HA vaccine is believed to induce fewer adverse reactions than conventional ones, but the risk remains. Caution should be exercised particularly in persons with allergic predisposition.[14,15] It is natural to avoid unnecessary vaccines as much as possible, and mass vaccinations of healthy children with a vaccine that is not able to prevent the onset of disease and epidemics should be discontinued.

We (physicians on the frontline) encounter repeated influenza epidemics despite annual mass influenza vaccinations and are deeply distrustful of the vaccine. Now that physicians avoid injections as much as possible even for the treatment of diseases, mass influenza vaccinations require a reevaluation.

In Practice of Pediatrics, a representative textbook on pediatrics in the United States, Loda et al. state that the influenza vaccine does not have the effect of controlling influenza but is recommended in children with cystic fibrosis, congenital heart disease, diabetes mellitus, asthma (excluding those with egg allergy), rheumatic heart disease, or other diseases.[16] If the influenza vaccine has the ability to reduce the severity of influenza, vaccinations of high-risk children are beneficial. However, clear evidence for the benefit is lacking. As described previously, Oda is skeptical about the benefit.

At any rate, we (physicians administering vaccine on the frontline) believe that mass influenza vaccinations of healthy children should be suspended and that efforts should be made to develop more effective live vaccines.

Summary

During the influenza B epidemic from February to March 1977, we surveyed the incidence in elementary schools, kindergartens, and childcare centers in Maebashi City to evaluate the efficacy of mass influenza vaccinations in the epidemic in the population.

1. Mass vaccinations were provided at all elementary schools, with the vaccination rate ranging from 57% to 100%.
2. The proportion of absentees during the period was not correlated with the vaccination rate.
3. Analysis of the time of the onset of epidemic and geographical conditions showed no evidence that elementary schools with low vaccination rates played a leading role in the spread of epidemic.
4. Mass vaccination was not performed at about half the childcare centers and kindergartens. The vaccination rate at facilities with mass vaccination ranged from 30% to 80%.
5. There was no correlation between the vaccination rate and the incidence.
6. The degree of the epidemic in kindergartens and childcare centers without mass vaccinations was similar to that in facilities with a vaccination rate of 70% or more.
7. Taken together, mass influenza vaccinations were unlikely to prevent or reduce the influenza epidemic in the year.
8. We discussed the significance of mass influenza vaccinations in schools and recommended its discontinuation and investigation.

Finally, we thank the officials at the Maebashi Health Division for providing data. The abstract of

this article was reported at the 73rd Discussion of the Gunma Meeting of the Japan Pediatric Society.

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(This article was reported in the Gunma Prefectural Medical Bulletin. 1977;350:16.)

[Appendix 2] Adverse reaction after the first dose of the influenza vaccine in Maebashi City in November 1979

The onset of this case, the course of symptoms, and actions taken were summarized in a report on vaccine-related health hazards and sent from the city to the prefecture on March 11, 1980. A notification dated August 11, 1980, was forwarded from the mayor of Maebashi to the director of the Maebashi Health Center, the governor of Gunma Prefecture, and the Ministry of Health and Welfare. A written claim on health care costs and medical treatment together with attached documents was sent to the adjudication subcommittee of the communicable disease prevention committee for review. This is summarized as follows.

(1) Name of the vaccinee: T.I. (born on June 23, 1968), a Grade 5, Class 3 student in Maebashi municipal J elementary school
(2) Vaccine: Influenza HA vaccine (manufacturer, K laboratory; date of manufacturing, October 9, 1979; date of testing, October 9, 1979; lot number, 113)
(3) Details of health hazards
a. **Initial symptom**: Convulsive seizure during sleep on the night of vaccination
b. **Past history**: The student underwent surgery for diaphragmatic hernia at the age of 5 months. Around 4 p.m. on Thursday, September 27, 1979, the student failed to hang on to an overhead

ladder and fell when playing in the schoolyard after school. The student fell on his left arm and failed to bear the weight, resulting in incomplete fracture of the left forearm (the distal end of the radius). There was no evidence of a head bruise or falling because of unconsciousness or seizure. The student had no past history of convulsive seizures.

c. **Family history**: The family consisted of the father (janitor of elementary school), mother (homemaker), and a brother (first-year high school student). No significant history was found.

d. **Date of vaccination and the course after vaccination**

The student received the first dose of the influenza vaccine (unscheduled) at Maebashi municipal J elementary school at around 2 p.m. on November 15, 1979. After the vaccination, the student attended regular classes, went home, and went to bed at 21:00. Around 22:30, the convulsive seizure occurred. The seizure lasted approximately 1 minute without fever. The second convulsion occurred at 22:30 on December 9. Convulsive seizures recurred at 22:30 on December 15 (for 2 minutes 30 seconds), and the student was brought by ambulance to a Maebashi municipal nighttime emergency clinic for clinical examination. As instructed by the treating physician, the student went to the Department of Neurosurgery, Gunma University Hospital, on December 17, and underwent radiography of the head and electroencephalography on December 19. The student received a diagnosis of convulsive seizure and treatment with anticonvulsants. The student was examined at the Department of Pediatrics, Gunma University Hospital, on January 23, 1980 and underwent again computed tomography of the head and electroencephalography at the Department of Neurosurgery, Gunma University Hospital, on February 14.

[Examination results]

The details of the examination results were unclear. According to the medical certificate, electroencephalography on December 19, 1979, showed sporadic paroxysmal discharge in the right hemisphere, and computed tomography of the head on February 14, 1980, showed no abnormalities. Electroencephalography on the same day showed less paroxysmal discharge.

(4) Review process and results at the vaccine-related health hazard investigation committee in Maebashi City

On May 7, 1980, the vaccine-related health hazard investigation committee in Maebashi City was called for review of this case, and an interim report was compiled as follows. The committee was not yet ready to draw a conclusion because it did not have sufficient data on the cause of injury before vaccination, its impact, and other past history to determine whether the symptoms after the vaccination were caused by the vaccination and because it would be desirable to perform the third electroencephalography to observe and investigate in detail the course of symptoms of the victim. Thus, the committee would like to review the case after those data were available and then make a final decision. The case was tabled for further deliberation.

As instructed by the first health hazard investigation committee, the city collected relevant data. Meanwhile, the student had the fourth convulsion on the night of May 21, went to the Department of Neurosurgery, Gunma University, for examination on May 22, and underwent the third electroencephalography on May 30.

The second investigation committee was called on July 9, and the following conclusions were reached. Review of data on the past history and underlying illness of the victim before the influenza vaccination revealed no previous convulsions (central nervous system symptoms). A relationship to the vaccination cannot be ruled out because the symptom occurred on the day of the vaccination. This case should be examined by the adjudication subcommittee of the communicable disease prevention committee, the Ministry of Health and Welfare.

(5) The Minister of Health and Welfare notified the mayor of Maebashi on March 20, 1981, that the case was not attributed to the vaccination because of the following reasons. The patient received the influenza vaccine on November 15, 1979, and had convulsive seizures on the night. The symptom on the day of the vaccination was limited to a convulsive seizure with no symptoms of encephalitis or encephalopathy. In consideration of the subsequent course, the case was genuine epilepsy and unlikely to be caused by the influenza vaccination.

(6) After receiving the notification, the city officials, responsible board members of the Maebashi Medical Association, and health hazard investigation committee members held an emergency meeting on April 14, 1981. The majority of participants believed that the city should make

administrative decisions to provide some relief measures, and the city decided to offer a solatium. The view of the vaccination committee of the Maebashi Medical Association on this case is as follows. (1) The municipal health hazard investigation committee conducted detailed surveys on this case twice and concluded that a relationship to the vaccination cannot be ruled out. The Ministry of Health and Welfare determined that the case was genuine epilepsy with no grounds. To medically elucidate the case, the committee wanted the ministry to disclose the reason for the denial. (2) According to precedents, however, the ministry is unlikely to disclose the reason. If the committee makes an objection, the process is time-consuming, and the victim will not benefit from it. If the city implements a relief measure when in doubt, the committee may as well bring this case to an end. (3) If the city implements relief measures by itself, the committee is willing to cooperate on a future vaccination program with a sense of security.

[Appendix 3] Survey on epidemics of influenza-like illness and class closure at the Aramaki Elementary School

Maebashi Municipal Aramaki Elementary School   Chieko Takarada (nursing teacher)
Masako Suzuki (school physician)

I. Introduction

This school is one of the designated schools selected by the Maebashi Research Group for the Study of Influenza Epidemics and has been paying special attention to influenza epidemics. A large type B epidemic occurred in January 1985, which required closure of 17 of 21 classes at the school. Class closures are determined with consideration of the absentee rate, proportion of attending children with fever, and epidemic situations at the school level. However, the efficacy of class closure varies; the absentee rate is high in some classes and 0% in other classes after resumption of classes. This may reflect our difficulties in monitoring the incidence during the class closure period and taking appropriate actions. We surveyed the absentees and fever during this epidemic to characterize the epidemic and implement effective class closures in the future.

II. Subjects and methods

1. Survey period: 27 days from January 14 (Mon) to February 9 (Sat), 1985
2. Daily absentee records were used as reference materials to investigate the absentee rate in all schoolchildren (800 persons). Children absent because of obvious accidents and other diseases were excluded to accurately identify those absent because of influenza-like illness as much as possible.
3. During the survey period, a survey form shown in Table 1 was distributed to children who had fever and common cold symptoms and completed by their parents for subsequent analysis.

III. Results

1. School conditions

(1) The epidemic course and the absentee rate at the school (Figure 1)
On January 17 (Thu), the school absentee rate exceeded 2%, which showed a sign of epidemic. The rate was 4% on January 19 (Sat) and rapidly increased to 11.9% on January 21 (Mon), resulting in closure of 2 classes. On January 22 (Tue), the absentee rate peaked at 15.5% (119 of 721 enrolled children excluding those in the 2 closed classes), requiring closure of 8 classes. The absentee rate ranged from 13% to 15% from January 23 to 30 (Wed), with a total of 17 classes closed. In February, the absentee rate rapidly decreased, and the epidemic almost ended after the consecutive holidays of February 10 (Sun) to 11 (Mon).

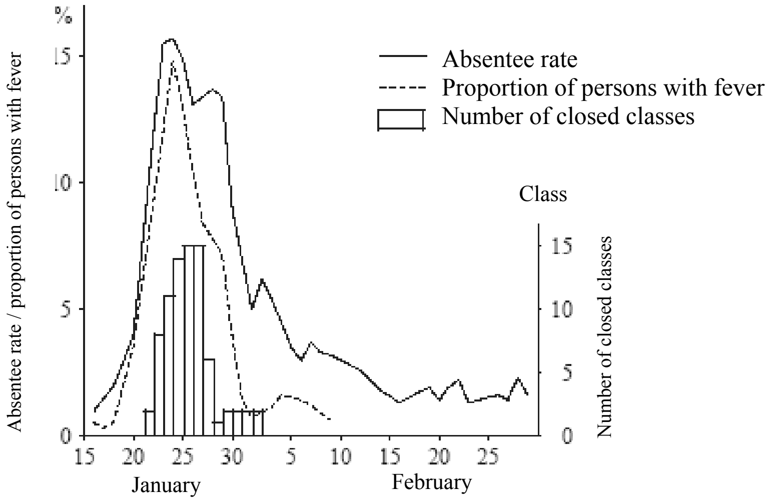

Figure 1. The Epidemic Course and the Absentee Rate at the School.

Table 1. Absentee Survey Form.

To parents

Maebashi Municipal Aramaki Elementary School
Principal Reijiro Takebuchi

The Absentee Questionnaire below is used to characterize this epidemic of the common cold and develop preventive measures against epidemics for the future. Complete and submit this form. Thank you for your cooperation.

Absentee Questionnaire

Grade Class boy / girl	Name of child	Name of parents

Circle all appropriate items and fill in the parentheses.

1. Fever: No / Yes Highest temperature °C
(Temperature of 37.5°C or more from January__ to__)

2. Cough: No / Yes (Mild, Moderate, Severe, from January__to__)

3. Other symptoms
Feeling sick, Loss of appetite, Nausea, Vomiting, Headache, Sore throat
Muscle / Joint ache, Nose bleed, Rash (eruption), Ear ache

4. Medical attention: No / Yes
(Diagnosis)

5. Any other family members with similar symptoms No / Yes
* Please specify who (in the margin as needed)
From January__to__

(2) Relationship between the absentee rate and the proportion of persons with fever (Figure 1)

The survey form was used to identify persons with a temperature of 37.5°C or more, and the proportion of persons with fever was presented with a dotted line. The proportion of persons with fever was similar to the absentee rate before the epidemic peak but much lower than the absentee rate after the peak. It seemed that symptoms such as cough and general malaise persisted after fever (a feature of acute disease) resolved and that children were absent until they got their strength back.

2. Epidemic conditions by grade

(1) Incidence by grade (Table 2)

The majority of children in each grade had common cold-like symptoms and fever. The incidence was high particularly in younger children (first and second graders).

Table 2. The Number of Enrolled Children and the Proportion of Children with Common Cold-Like Symptoms in Each Grade.

Grade	1	2	3	4	5	6	Total
Number of enrolled children	114	119	136	135	142	154	800
Number of children with common cold-like symptoms	84	87	70	84	72	71	468
Incidence (%)	73.7	73.1	51.5	62.2	50.7	46.1	58.5

(2) Absentee rate and proportion of persons with fever (Figure 2)

The absentee rate was high at 65% in first and second graders and lowest at 41.6% in sixth graders. The proportion of persons with fever was higher than 50% in first and second graders and 37% in sixth graders. In fourth graders, the proportion of persons with fever exceeded the absentee rate. These persons probably included children going to school despite fever, children who went to school and then noticed fever, and children who had fever after leaving school.

(3) Duration of fever (Figure 3)

The duration of fever ranged from one to eight days. The distribution peaked at two or three days in first to fifth graders but at four days in sixth graders.

(4) Highest temperature (Figure 4)

The proportion of children with a highest temperature of 39°C or more was highest in first, second, third, and fourth graders. This trend was particularly evident in first, second, and fourth graders in whom the proportion of children with fever was particularly high. No specific trend was found in fifth graders or sixth graders.

A temperature of 38°C or more is generally used as a diagnostic criterion for influenza. At schools, temperatures up to 37.3°C are considered normal in children, and thus children with a temperature of 37.5°C or more were considered persons with fever in the present survey. It may be controversial whether children with highest temperatures of 37.5°C to 37.9°C had influenza or similar diseases in the present survey.

(5) Relationship between absentees and fever (Figure 5)

In Figure 5, bar charts above the zero line indicate the absentee rate, and those below the zero line indicate the attendance rate. Shaded areas indicate the proportion of persons with fever. The majority of absentees had fever. The proportion of persons with fever was highest in children in grade 5, class 3 (90%) and lowest in grade 2, class 1 (42%). A small number of children attending classes had fever. These children included those who went to school despite fever and those who noticed fever after going to school; 95% of persons with fever were absent.

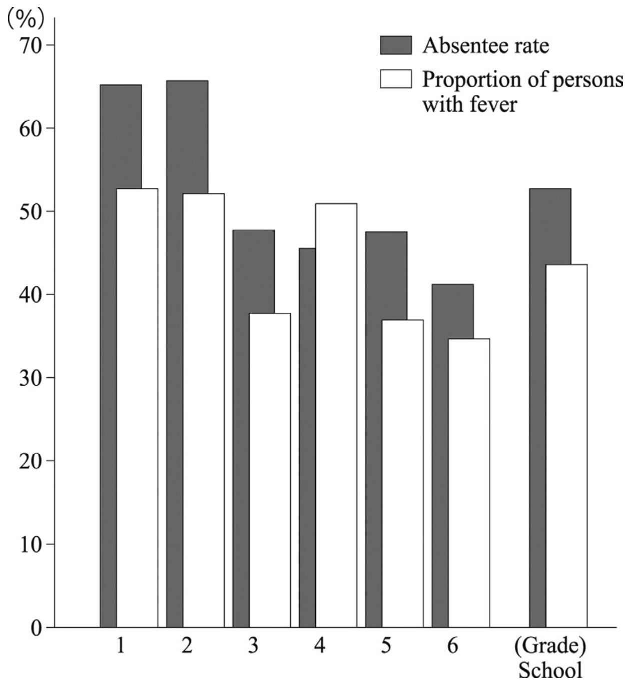

Figure 2. The Rate of Common Cold-Related Absentees and the Proportion of Persons with a Temperature of 37.5°C or More by Grade.

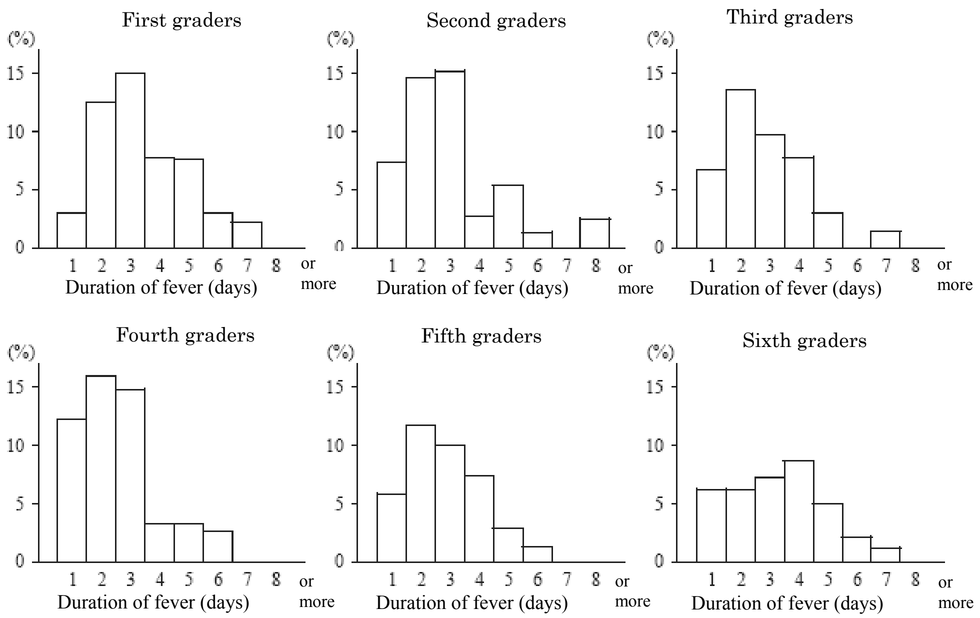

Figure 3. Duration of Fever (Temperatures of 37.5°C or More).

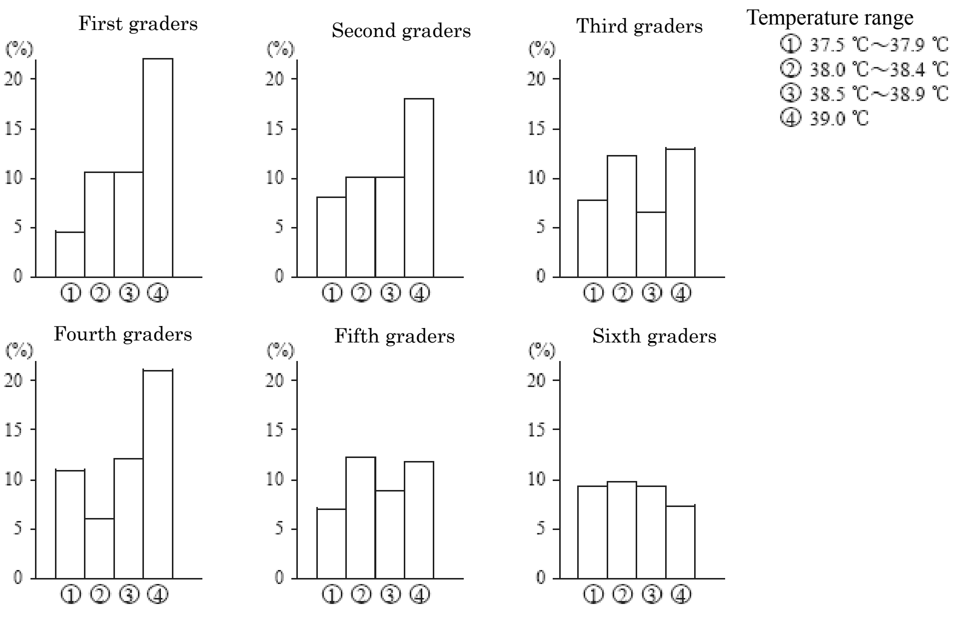

Figure 4. Distribution of Highest Temperatures (Percentage to the Number of Enrolled Children).

3. Class-specific epidemic conditions

(1) Spread of the epidemic (Table 3)

Days on which the absentee rate peaked in individual classes were identified in Figure 6 and listed. On January 21 (Mon), grade 2 class 1 with a peak absentee rate of 26% and grade 6 class 2 with a peak absentee rate of 29% were closured. From January 22 to 26 (Sat), 17 classes had peak absentee rates and were closed. Grade 2 class 2 had a peak absentee rate of 22% and was closed on January 22. When the class was resumed on January 28, the absentee rate was 25%. The routes of infection (grades, school building, and doorways) could not be identified.

Table 3. List of Dates When the Absentee Rate Peaked in Individual Classes.

Date	January 21 (Mon)	22 (Tue)	23 (Wed)	24 (Thu)	25 (Fri)	26 (Sat)	28 (Mon) or later	
Class having a peak absentee rate (grade-class)	2-1	2-2	1-1	3-1	1-2	5-1	1-3	
	6-2	3-2	2-3	5-3	4-1		4-3	
		3-3	6-4	5-4			5-2	
		4-2					6-3	
		4-4						
		6-1						
Number of classes (total)	2	6	3	3	2	1	4	21

(2) Epidemic conditions during class closure (Figure 6)

Attempts were made to estimate the incidence during the survey period from fever and other clinical symptoms documented on the survey form. In Figure 6, the absentee rate is indicated by the solid line, and the proportion of persons with fever is indicated by the dotted line for each class. Dates when class closure was started and ended are indicated by circles on the absentee line.

Epidemic conditions during class closure varied. Some classes had a reduction in the proportion of persons with fever after closure, few new patients, and no persons with fever after class resumption (grade 1 class 3, grade 4 class 4, and grade 6 classes 1, 2, and 3). Other classes had an increase in the proportion of persons with fever after class closure and similar absentee rates after class resumption (grade 1 class 1, grade 1 class 2, grade 2 class 1, grade 3 class 3, grade 4 class 2, and grade 5 class 3). Grade 2 class 2 had an increase in the absentee rate after class resumption.

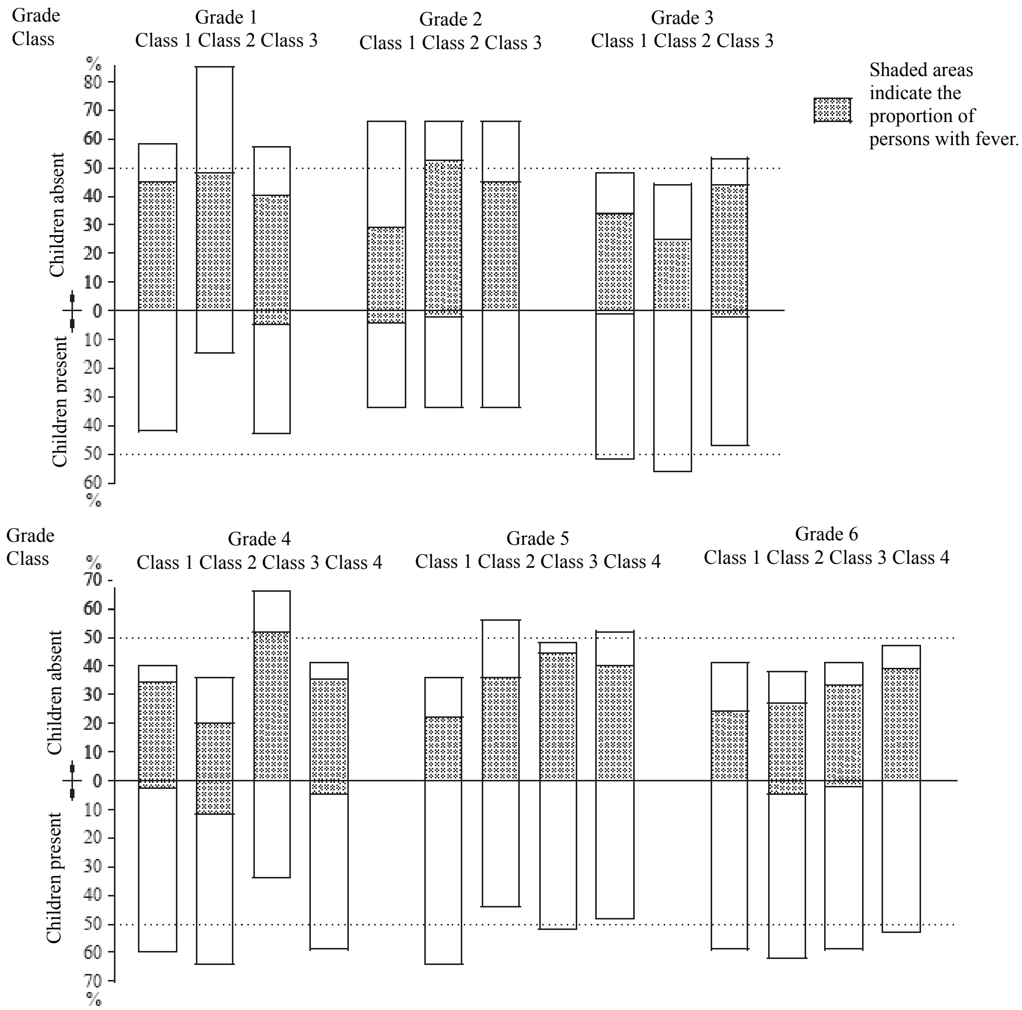

Figure 5. The Absentee Rate and the Proportion of Persons with a Temperature of 37.5°C or More in Each Class.

(3) Conditions of classes without closure

As shown in Figure 6, four classes remained opened including grade 4 class 1, grade 4 class 3, grade 5 class 1, and grade 5 class 2. In all four classes, the peak absentee rate exceeded 20%, a criterion for class closure. The absentee rate in grade 5 class 2 reached 33.3% on January 25 (Fri). During the period, the absentee rate increased to 66.7% in grade 4 class 3 and 55.5% in grade 5 class 2 (Figure 5).

These four classes were not closed because of different reasons. In grade 5 class 2, the absentee rate was 33.3% on January 25 (Fri), and a decision was to be made on the following day, when the rate decreased below 20%. In grade 4 class 3, the absentee rate was relatively high on consecutive days. When the absentee rate exceeded 20%, the epidemic at the school was about to end, and two-thirds of children in the class had been infected. It was determined that the absentee rate was unlikely to increase further. In grade 4 class 1 and grade 5 class 1, the absentee rate reached 22%, and a decision was to be made on the following day, when the rate decreased.

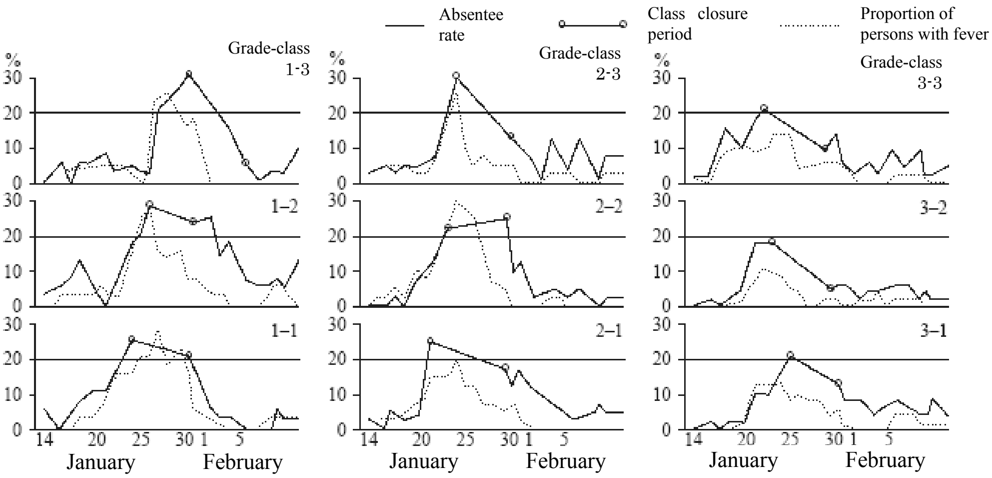

Figure 6-1. Curves for the Absentee Rate and the Proportion of Persons with a Temperature of 37.5°C or More in Each Class.

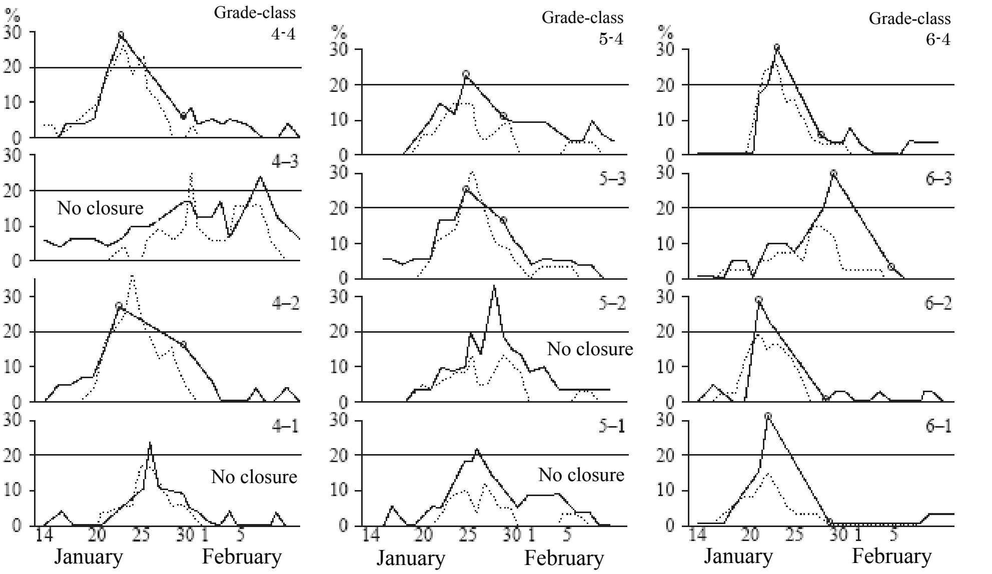

Figure 6-2. Curves for the Absentee Rate and the Proportion of Persons with a Temperature of 37.5°C or More in Each Class.

4. Change in the absentee rate after class closure

(1) Relationship between the number of days of class closure and the change in the absentee rate (Figure 7)

The number of days of class closure ranged from 4 to 6 days; 5 classes were closed for 4 days, 10 classes were closed for 5 days, and 2 classes were closed for 6 days. Except for 1 class, class closure was effective in reducing the absentee rate after classes were resumed, regardless of the number of days of class closure. There was no clear correlation between the duration of closure and the efficacy.

(2) Relationship between the timing of the start of class closure and the change in the absentee rate (Figure 8)

The peak of each curve of the proportion of persons with fever in Figure 6 was considered to be the actual epidemic peak in each class, and the relationship between the peak day and the start of closure was classified into the following categories A, B, and C to compare the change in the absentee rate after the end of closure.

A: The proportion of persons with fever peaked during closure (6 classes).

B: The proportion of persons with fever peaked on the day before closure (8 classes).

C: The proportion of persons with fever peaked at least 2 days before closure (3 classes).

Compared with categories B and C, category A had slightly lower absentee rates at the start of closure and less reductions in the absentee rate after the end of closure. Categories B and C had considerably high absentee rates at the start of closure and substantial reductions in the absentee rate after the end of closure.

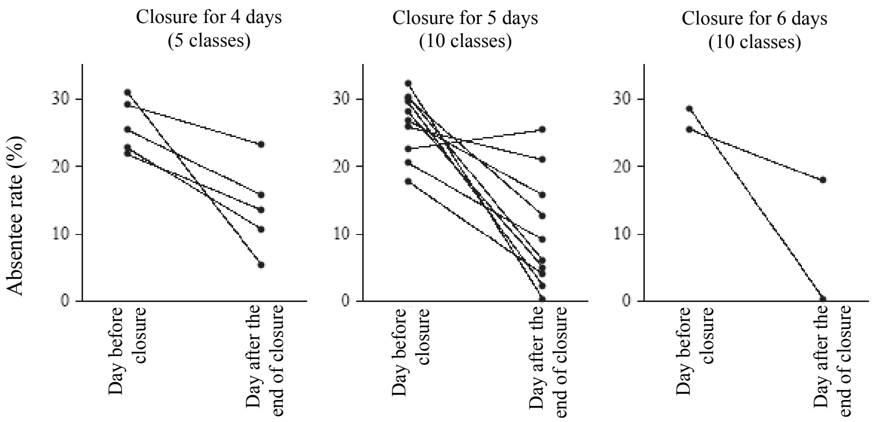

Figure 7. Relationship between the Duration of Closure and the Change in the Absentee Rate.

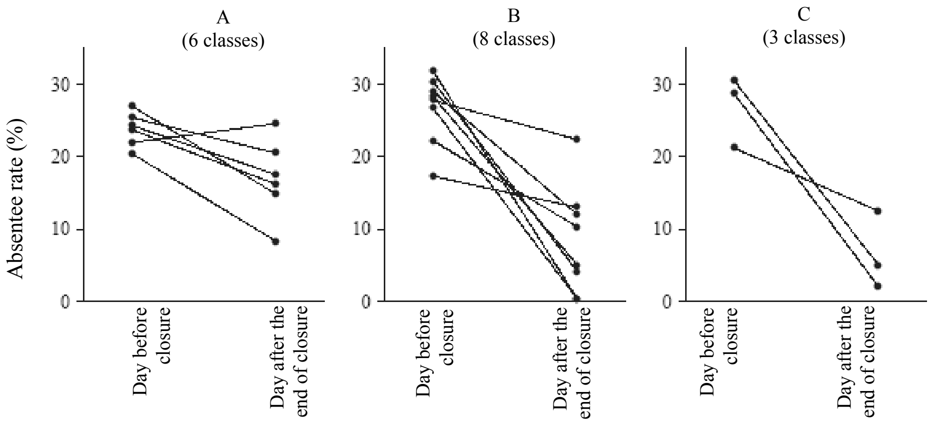

Figure 8. Relationship between the Timing of the Start of Class Closure and the Change in the Absentee Rate.

IV. Summary and Discussion

1. The present epidemic at our school was associated with many outbreaks during a relatively short period from mid January to early February, and 17 of 21 classes were closed. The school absentee rate at the peak season was as high as 15.5%.

2. First and second graders had higher absentee rates and higher proportions of persons with fever than other graders and were more severely affected by the epidemic.

3. Fever (defined as a temperature of 37.5°C or more) often lasted for two to three days. First, second, and fourth graders were more likely to have high fever (highest temperatures of 39°C or more) and somewhat severe disease.

4. Analysis of the absentee rate and the proportion of persons with a temperature of 37.5°C or more showed that 95% of persons with fever were absent and that 70% of absentees had fever.

5. Class closures for four, five, and six days were similarly effective in reducing the absentee rate.

6. In classes that were closed immediately after the absentee rate exceeded 20%, reduction in the absentee rate after the end of closure was insufficient.
7. If the proportion of persons with fever on the day after closure, which is measured by some method, is higher than that on the day of closure, the absentee rate after the end of closure is unlikely to decrease substantially.
8. To implement an effective class closure, the decision on whether to close a class should be made one day after the absentee rate exceeds 20%.

Findings from this epidemic cannot be generalized because the epidemic pattern of influenza varies from year to year. Above all, it is necessary to continue learning and exercise to strengthen mental and physical health according to health education and implement proactive and careful preventive measures every year.

[Appendix 4] Major activities of the research group for the study of influenza (research progress)

This is a chronological table of activities from the formation of the research group to the plan and review of this report, a summary of the five-year survey. While drafting this report, the research group is determined to continue its activities. The group is analyzing and investigating in more detail the existing data and working to address the next challenges.

(Meetings for information collection and data analysis are excluded.)

Date	Activity	Description
December 8, 1980	Study group meeting on the efficacy of mass influenza vaccination (Tokyo) (Group leader: Akira Oya, director of the Virus Rickettsia Division, National Institute of Infectious Diseases)	Yoshikazu Kanazawa and Hideaki Yagi (directors of the Maebashi Medical Assosication, now a group members) at the Maebashi Medical Association attended the meeting and proposed a survey on the efficacy of the influenza vaccines and epidemics.
January 9, 1981	Vaccination committee of the Maebashi Medical Association	Investigation of the efficacy of the influenza vaccines Akira Oya, director of the Virus Rickettsia Division, National Institute of Infectious Diseases attended.
March 12, 1981	Vaccination committee of the Maebashi Medical Association	Planning of a survey on the efficacy of the influenza vaccines and epidemics
April 23, 1981	Formation of the research group for the study of influenza	Commission of group members, briefing on the plan and objectives of a survey on the efficacy of the influenza vaccines and epidemics, selection of Shuzo Yugami as the director
June 17, 1981	Meeting of the research group for the study of influenza	Discussion of the plan of the survey
June 25, 1981	Meeting with nursing teachers of the five designated schools	Discussion of practical problems and implementation of the plan
July 16, 1981	Meeting with nursing teachers of the five designated schools	Planning of blood sampling
August 19, 1981	Meeting of the research group for the study of influenza	Discussion of measures for the meeting with nursing teachers, establishment of the outline of the blood sampling plan
October 2, 1981	Meeting with principals of the five designated schools	Briefing on the objectives of the planned survey and asking for cooperation
October 6, 1981	Meeting with nursing teachers of the five designated schools	Discussion of the details of the blood sampling plan
October 15, 1981	Meeting of the research group for the study of influenza	Final check of the blood sampling plan
November to December 1981	Blood sampling from second graders of the five designated schools	Pre-epidemic blood sampling in the first fiscal year

Date	Activity	Description
December 9, 1981	Meeting of the research group for the study of influenza	Discussion of electronic processing and review of anemia test results
January 12, 1982	Submission of grant application for the Toyota Foundation Second Research Contest	
February 10, 1982	Meeting of the research group for the study of influenza	Report on winter epidemics in the first fiscal year (1981 to 1982), discussion of research for the future, discussion of the blood sampling plan after epidemics in the fiscal year
March 24, 1982	Blood sampling from second graders of a designated school	Blood sampling after epidemics in the fiscal year (at Utsuboi Elementary School alone)
March 27, 1982	Submission of protocol for the Toyota Foundation Second Research Contest grant program	
April 3, 1982	Briefing session on the Toyota Foundation Second Research Contest grant program (Tokyo)	
April 22, 1982	Meeting of the research group for the study of influenza	Review and discussion of survey results of winter epidemics in the first fiscal year (1981 to 1982)
May to June 1982	Blood sampling from third graders of 4 designated schools	Blood sampling after epidemics in the first fiscal year
June 17, 1982	Meeting of the research group for the study of influenza	Analysis and discussion of the results of antibody titers testing in the first fiscal year and review of the results of blood sampling in the first fiscal year Inspection by the Toyota Foundation review committee
August 11, 1982	Meeting of the research group for the study of influenza	Analysis and discussion of the results of antibody titer testing in the first fiscal year
August 20, 1982	Submission of a protocol for the Toyota Foundation Second Research Contest grant program	
August 28, 1982	Presentation of the Toyota Foundation Second Research Contest grant program (Tokyo)	
September 20, 1982	Submission of a notification of preliminary research completion for the Toyota Foundation Second Research Contest grant program	
October 12, 1982	Meeting of the research group for the study of influenza	Confirmation of the plan for the second fiscal year, planning of blood sampling, report on the awarding process of the Toyota Foundation Second Research Contest Silver Award
October 13, 1982	Ceremony for the Toyota Foundation Second Research Contest Silver Award and grant program	
October 15, 1982	Submission of a spending plan for the Toyota Foundation Second Research Contest grant program	
October 28, 1982	Meeting with nursing teachers of the five designated schools	Discussion of practical problems for implementation of the plan for the second fiscal year and details of blood sampling plan
November 1982	Blood sampling from third graders of the five designated schools	Pre-epidemic blood sampling in the second fiscal year
December 8, 1982	Meeting of the research group for the study of influenza	Discussion of the results of total cholesterol testing and methods for a statistical survey on cause-specific mortality
February 9, 1983	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the second fiscal year (1982 to 1983)

Date	Activity	Description
April 13, 1983	Meeting of the research group for the study of influenza	Interim report on winter epidemics in the second fiscal year (1982 to 1983)
April 16, 1983	Study group meeting on prevention of influenza (Tokyo)	Report on the winter epidemic survey results in the second fiscal year (1982 to 1983), report on epidemic survey results in the third fiscal year (1983 to 1984)
April 27, 1983	Meeting with nursing teachers of the five designated schools	Arrangement of the details of blood sampling after epidemics in the second fiscal year
May to June 1983	Blood sampling from fourth graders of the five designated schools	Blood sampling after epidemics in the second fiscal year
June 9, 1983	Meeting of the research group for the study of influenza	Discussion of lipid test results in persons with abnormalities in total cholesterol levels, review of the results of blood sampling in the second fiscal year, determination of the supplementary testing (mumps) in the third fiscal year
August 2, 1983	Meeting with principals of the five designated schools	A proposal was made to distribute a summary of progress and interim reports for the first and second fiscal years.
August 17, 1983	Meeting of the research group for the study of influenza	Decision was made to prepare the Interim Report, a progress report for the first and second fiscal years. Inspection by the Toyota Foundation review committee
October 19, 1983	Meeting of the research group for the study of influenza	Analysis of the results of mumpus antibody titer testing in the second fiscal year, planning of pre-epidemic blood sampling in the third fiscal year
November 14, 1983	Interview with the Nikkei Medical	
November 27, 1983	Second interim report meeting for the Toyota Foundation Second Research Contest grant program (Tokyo)	
November 1983	Blood sampling from fourth graders of the five designated schools	Pre-epidemic blood sampling in the third fiscal year
December 14, 1983	Meeting of the research group for the study of influenza	Report on pre-epidemic blood sampling in the third fiscal year, report on anti-mumps antibody titers, determination of a survey on the relationship between influenza epidemics and climate conditions
December 17, 1983	Interview with the TBS	
February 20, 1984	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the third fiscal year (1983 to 1984), review of reports at academic meetings
April 14, 1984	Study group meeting on the prevention of influenza (Tokyo)	The study group on the prevention of influenza completed its scheduled activities. The group leader expressed his intention to continue activities in some manner.
April 17, 1984	Meeting of the research group for the study of influenza	Planning of blood sampling, approval of reporting at academic meetings and conferences
May 1984	Blood sampling from fifth graders of the five designated schools	Blood sampling after epidemics in the third fiscal year
May 8, 1984	Interim report meeting for the Toyota Foundation Second Research Contest (Tokyo)	
May 29, 1984	Submission of application for the fiscal 1984 Toyota Foundation Research Grant	
June 10, 1984	Reporting at the Gunma Meeting of the Japan Pediatric Society	Presentation of Influenza Epidemics in Maebashi City

Date	Activity	Description
June 19, 1984	Meeting of the research group for the study of influenza	Determination of distribution sites of an interim report, report on blood sampling after epidemics in the third fiscal year and presentation at the Gunma Meeting of the Japan Pediatric Society, and arrangement of presentations at academic meetings and conferences in the future
July 12, 1984	Reporting at the microbiology council study session (Maebashi)	Presentation of survey results by the research group for the study of influenza, broadcast by NHK News
July 17, 1984	Reporting at the Japanese Society for Virology (Sapporo)	Presentation of survey results by the research group for the study of influenza, interview with the Hokkaido Shimbun
August 3, 1984	Chiba City officials came to Maebashi City for survey.	
August 7, 1984	Meeting of the research group for the study of influenza	Determination of the supplementary testing (hemoglobin testing) in the fourth fiscal year, development of an annual activity plan for the research group for the study of influenza, additional distribution of the interim report to persons other than medical professionals to increase awareness, report on the Japanese Society for Virology
September 7, 1984	Submission of the fiscal 1984 Toyota Foundation grant research protocol	
October 8, 1984	The fiscal 1984 Toyota Foundation research grant was awarded.	
October 17, 1984	Ceremony for the fiscal 1984 Toyota Foundation research grant award (Tokyo)	
October 19, 1984	Meeting of the research group for the study of influenza	Planning of pre-epidemic blood sampling in the fourth fiscal year
November 1, 1984	Meeting with nursing teachers of the five designated schools	Discussion of the details of pre-epidemic blood sampling in the fourth fiscal year
November 1984	Blood sampling from fifth graders of the five designated schools	Pre-epidemic blood sampling in the fourth fiscal year
November 25, 1984	Research presentation at the Toyota Foundation Second Research Contest (Tokyo)	
December 11, 1984	Interview with the TBS	
December 12, 1984	Meeting of the research group for the study of influenza	Report on pre-epidemic blood sampling and the results of hemoglobin testing in the fourth fiscal year, report on the fiscal 1984 Toyota Foundation research grant report meeting, report on an interview with the TBS
February 13, 1985	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the fourth fiscal year (1984 to 1985), interim report on virus isolation, antibody titer testing, and antibody analysis, examination of the content of the group meeting to invite Yasue Takeuchi, manager of the Influenza Division, National Institute of Infectious Diseases
February 15, 1985	Meeting with Yasue Takeuchi, manager of the Influenza Division, National Institute of Infectious Diseases to exchange information	
February 17, 1985	Broadcast by the TBS	
March 30, 1985	Interview with a reporter from the Arts and Cultural News Department, Asahi Shimbun Head Office	
April 17, 1985	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the fourth fiscal year (1984 to 1985), planning of the project in the fifth fiscal year

Date	Activity	Description
April 22, 1985	Telephone interview with a reporter from Asahi Shimbun Head Office	
May 1, 1985	Meeting with nursing teachers of the five designated schools	Arrangement of the details of blood sampling after epidemics in the fourth fiscal year
May 1985	Blood sampling from sixth graders of the five designated schools	Blood sampling after epidemics in the fourth fiscal year
May 30, 1985	Submission of an interim report on the fiscal 1984 Toyota Foundation research grant program (first report)	
June 12, 1985	Meeting of the research group for the study of influenza	Report on blood sampling after epidemics and anti-mumps antibody titers in the fourth fiscal year, analysis of data from a survey on patients treated under the National Health Insurance
August 27, 1985	Meeting of the research group for the study of influenza	Analysis of antibody titer testing in the fourth fiscal year, discussion on the description of the elementary school version of educational primary information, report on the vaccine efficacy on absenteeism, report on a research council of the Kanto Koshinetsu-Sei School Health Conference
October 17, 1985	Meeting of the research group for the study of influenza	Planning of pre-epidemic blood sampling in the fifth fiscal year, analysis of antibody titers against influenza B virus, analysis of data on patients treated under the National Health Insurance
October 23, 1985	Meeting with nursing teachers of the five designated schools	Arrangement of the details of pre-epidemic blood sampling in the fifth fiscal year
November 1985	Blood sampling from sixth graders of the five designated schools	Pre-epidemic blood sampling in the fifth fiscal year
November 9, 1985	Research presentation for the fiscal 1984 Toyota Foundation research grant program (Tokyo)	
December 17, 1985	Meeting of the research group for the study of influenza	Pre-epidemic blood sampling in the fifth fiscal year, discussion of application for the fiscal 1985 Toyota Foundation outcome presentation grant
December 24, 1985	Submission of an interim research report on the fiscal 1984 Toyota Foundation research grant program (second report)	
February 19, 1986	Submission of an application for the fiscal 1985 Toyota Foundation outcome presentation grant	
February 20, 1986	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the fifth fiscal year (1984 to 1985), planning of blood sampling after epidemics in the fifth fiscal year, formation of an editorial committee for preparation of the 5-year final report
April 16, 1986	Meeting of the research group for the study of influenza	Analysis and discussion of winter epidemics in the fifth fiscal year (1984 to 1985), planning of future activities
June 18, 1986	Meeting of the research group for the study of influenza	Report on epidemics in Matsumoto area, report on the editorial committee for the fiscal 1985 Toyota Foundation outcome presentation grant report, discussion of the outline of the final report
July 18, 1986	Submission of an interim research report on the fiscal 1984 Toyota Foundation research grant program (third report)	
August 19, 1986	Meeting of the research group for the study of influenza	Vaccine survey by the Ministry of Health and Welfare, discussion of chapters and sections of the five-year final report

Date	Activity	Description
October 9, 1986	Interview with the TV Asahi	
October 15, 1986	The meeting was attended by Shuichi Hatano, professor and head of the Department of Epidemiology, the Institute of Public Health.	
October 21, 1986	Broadcast by TV Asahi	
October 22, 1986	Meeting of the research group for the study of influenza	Arrangement of new projects in the seventh fiscal year, report and review of the progress in preparation of the report on the fiscal 1985 Toyota Foundation outcome presentation grant, report on an influenza vaccine seminar hosted by the Consumers Union of Japan
October 28, 1986	Interview with and broadcast by the Nippon Television Gunma Station	
November 6, 1986	Interview with the NHK Maebashi Station	
November 11, 1986	Telephone interview with the Asahi Shimbun, Osaka Branch, telephone interview with a reporter in charge of the Ministry of Health and Welfare, Yomiuri Shimbun Head Office	
November 12, 1986	Broadcast by the NHK	
November 13, 1986	Interview with a reporter from the Komei Shimbun	
November 29, 1986	Interview with the Fukushima Television	

VI. Completion of the Survey

Atsuo Ujiiye, director of the Gunma Institute of Public Health

The efficacy of influenza vaccines is controversial. The Ministry of Health and Welfare and other proponents simply argue that the vaccine is the only method for protection against infection and do not discuss the original principle, that is, mass vaccinations of elementary and junior high school students should have efficacy in preventing epidemics and reducing the infection rate in high-risk groups, such as older individuals and patients. Many opponents simply argue that the vaccine is not effective because it does not prevent flu-like illness. Both parties focus on the protection at the individual level (they argue whether vaccinees are infected with influenza or not).

I believe that the currently available vaccines are more or less effective. However, the influenza vaccine is less effective than other vaccines and poorly effective when viruses with substantially different antigen structures circulate. It should be noted, however, that we are not concerned about those issues but administrative policies on vaccinations and related surveys.

The objective about 25 years ago (1962), when mass vaccinations of elementary and junior high school students started, was to prevent influenza epidemics by providing mass vaccinations of elementary and junior high school students, an age group amplifying influenza viruses. Thus, the policy is based on the major premise that epidemics are prevented and does not consider the protection of high-risk groups who are likely to die or develop serious conditions after infection. In light of the policy, elementary and junior high school students, who are not severely affected by infection, are annually vaccinated for protection of high-risk individuals against infection. Elementary and junior high school students are used as a shield. Actually, however, as migratory birds come annually, so do epidemics. It seems that adults are first affected by an epidemic in some seasons.

Elementary and junior high school students account for only one-seventh of the total population, and they are not the only group who live in a social life. Many adults now commute on crowded trains and naturally work together in the workplace. In addition, adults travel back and forth on business in the country, and persons who are infected first in each district are adults rather than elementary and junior high school students. Even if a highly effective vaccine were to be developed, it would be impossible to prevent epidemics by vaccination of elementary and junior high school students alone. It is easily conceivable from the yearly epidemics.

The research group of the Maebashi Medical Association is concerned about the effectiveness of administrative policies on vaccinations in the prevention of epidemics, not the protective efficacy of the vaccines against infection. Only Japan provides this type of mass vaccination and implements no preventive measures in high-risk individuals. High-risk individuals may receive the vaccine if they want. However, physicians are concerned about frequent adverse reactions in high-risk individuals and are responsible for those reactions. Thus, only a small number of physicians perform voluntary vaccination, and high-risk individuals do not receive the vaccine and are eventually neglected. Moreover, persons with significant symptoms are considered to have a contraindication and cannot be vaccinated in Japan.

In other countries, mass vaccinations are not employed, but patients and older individuals are encouraged to receive the vaccine on a voluntary basis. Differences in these issues between Japan and other countries are described below. In 1980, the Center for Disease Control (CDC) in the United States recommended influenza vaccination in the following conditions:

(1) Congenital and acquired heart failure
(2) Chronic pulmonary dysfunction
(3) Chronic kidney disease
(4) Diabetes mellitus and metabolic disease with increased susceptibility to infection
(5) Chronic severe anemia
(6) Immunodeficiency in patients with malignancies and patients treated with immunosuppressants
(7) In addition, older individuals 65 years or older and socially essential professionals at an

increased risk for exposure to infection

Hannoun at the Pasteur Institute in France identifies an age-related factor and considers persons 45 years or older, particularly older individuals 65 years or older, a high-risk group.

(1) Medical risk: Cardiovascular disease, bronchopulmonary disease, renal diseases (such as nephritis, nephrosis, kidney infection, patients undergoing hemodialysis, and patients with renal transplants), metabolic abnormalities (diabetes mellitus, Addison's disease), pregnant women, and others

(2) Socioeconomic risk: Socially or economically essential professionals who are exposed to infection such as physicians, paramedical staff, and persons who engage in transport, postal service, and communication service.

Marcus E. A., et al. in the Netherlands consider patients with the following diseases high-risk groups in terms of vaccination: chronic cardiopulmonary disease, neurological disorders resulting in respiratory disorder, chronic renal disease, chronic metabolic disease, repeated furuncle, other staphylococcal infections, and debility.

Other examples in foreign countries are omitted, and Japanese conditions are described. In Japan, emphasis is placed on contraindications rather than indications. The vaccine is contraindicated in patients with an acute, exacerbating, or active phase of cardiovascular disease, renal disease, and liver disease, pregnant women, and others who are ineligible to receive the vaccine.

As described above, too many contraindications raise concern about compensation for adverse reactions, and the vaccination of high-risk individuals is considered an exceptional indication. Only Japan has indications completely different from those in other advanced countries with a similar level of medicine. However, no specific adverse reactions in such high-risk groups have been reported in countries other than Japan. Japan appears to pay too much attention to adverse reactions in high-risk groups and to take the wrong approach. Given generous compensations in the country, it is understandable.

Interested in the Japanese unique policy on influenza prevention, investigators in the United States came to Japan to evaluate the efficacy of mass vaccinations of elementary and junior high school students a few years ago. At the same time Maebashi City decided to discontinue vaccinations. Experts at the CDC and NIH came to Japan and met officials of the Ministry of Health and Welfare and prevention groups. Their evaluations were published later (Walter R Dowdle, J Donald Miller, Lawrence B Schonberger, Francis A Ennis, and John R LaMontagne. Influenza Immunization Politics and Practices in Japan. The Journal of Infectious Diseases. 1980; 141: 258–264). The paper is full of bitter criticisms. They argued that it is no use discussing efficacy without controls. The conclusions are cited below.

The Japanese program for immunizing schoolchildren annually against influenza has been implemented with efficiency and imagination. As an outgrowth of the program, Japanese officials have established a national surveillance system for epidemic diseases in schools that should serve as a model for many other countries. In addition, the Japanese have developed a far-reaching program to compensate individuals in the event of adverse reactions to vaccinations.

Evidence supporting the benefit of influenza vaccinations is derived from special studies indicating a 50%–95% reduction in influenza-like disease among recipients of killed vaccine when the epidemic strain was similar to the vaccine strain.

Periodic epidemics that continue to occur are attributed by the Japanese to antigenic drift and shift of influenza viruses and the unavoidable lag in production of new vaccines. Varying degrees of efficacy and periodic epidemics of influenza in schools and communities would be expected and do not necessarily rule out positive benefits of vaccination. It is not known what the epidemic patterns of influenza might have been in the absence of the program; therefore, it is not possible to estimate accurately the effect of the program on transmission, morbidity, and mortality. The effect of the school immunization program, if not dramatic, could be significant; we have no basis for judgment.

The difficulty in obtaining proof of amelioration of influenza epidemics illustrates problems commonly experienced in evaluating recommended and public-sanctioned control measures for influenza. In the United States, ethical considerations preclude an objective assessment of the efficacy of influenza immunization in the high-risk groups for whom vaccine is recommended. In the absence of controlled trials in these groups, vaccine recommendations for high-risk persons have been based on evidence of protection derived from short-term trials in other populations. There is no proof that annual vaccination significantly reduces influenza-related deaths.

The Japanese experience poses many questions regarding a similar national school vaccination program in the United States. It is unlikely that the United States could surpass the achievements of Japan as to the proportion of children immunized each year. Even if we could, a positive impact of such a program could not be confidently predicted. Whether considering an annual vaccination program for schoolchildren or adults, data from careful, long-term studies are required. The present lack of data on the effect of annual vaccination on reduction of influenza-associated morbidity and mortality makes it difficult to establish reasonable program expectations or to measure accurately program achievements.

Given the conclusions, you may understand that Japanese influenza researchers see Maebashi City as a valuable control area.

Before Maebashi City discontinued mass vaccinations, Usui-gun, including Annaka City, discontinued vaccinations because of doubts about the efficacy and potential adverse reactions but experienced no greater epidemics thereafter. Independently of the discontinuation in Annaka City, a few physicians discussed the vaccine efficacy for a few years before discontinuation in Maebashi City. They focused on the efficacy in protecting individuals.

Because of the reasons described in this report, Maebashi City discontinued vaccinations. The chairperson of the prefectural communicable disease prevention and control committee (the president of the Gunma Medical Association) said at the end of the committee held at that time that the decision on whether to provide influenza vaccinations was left to the discretion of each municipal medical association. A responsible board member of the Maebashi Medical Association at that time was impressed by the decision that the issue should be at the discretion of each municipal medical association. Looking back on those times, he said that the rational attitude gave great momentum to subsequent development.

The Maebashi Medical Association did not simply discontinue vaccinations but also planned a survey to determine the effect of discontinuation on subsequent epidemics. I had been involved in vaccinations and thus participated in the survey as a research group member. As described in this report, five elementary schools were chosen as designated schools for a seroepidemiological survey with consideration of appropriate geographical conditions. Blood was collected biannually (November and May) from each of a total of approximately 600 children over a period of five years until second graders (in fiscal 1981) graduated from elementary schools to measure HI antibody titers and others. Infections were identified on the basis of symptoms as well as an increase in antibody titer, which were used for the planned epidemic survey.

The Gunma Medical Association supported the policy, and about half the municipal medical associations agreed with the Gunma Medical Association and participated in the survey. Although each of these associations surveyed a small number of children (40 persons), they started surveys in the same way as that used by the Maebashi Medical Association. The survey is gradually losing momentum because of a small number of subjects (40) and the lack of a leading study group. At any rate, the survey results are now being analyzed. I expect interesting results if things go as initially planned.

The Gunma Medical Association conducted a survey in vaccinated areas and non-vaccinated areas separately, which was an epoch-making attempt at that time. Naturally, Maebashi City and the Gunma Medical Association asked me to perform serum antibody testing. The Gunma Medical Association had two different viewpoints. I found that senior officials at the Gunma Medical Association had foresight and were highly knowledgeable, and thus I gladly followed the Gunma Medical Association's policy and accommodated its request. Because no specific budget was provided, I considered it is an informal request and decided to perform the testing as a part of our studies. Above all, I accepted the request partly because I was inspired by the enthusiasm of the Maebashi Medical Association for pursuing the truth.

During the survey, I came to realize that the Gunma Medical Association had the basic policy to provide vaccinations in principle and that it reluctantly accepted two viewpoints because it could not change the Maebashi Medical Association's determination to discontinue vaccinations. Whatever the background, it was easier for me to support the association with two viewpoints. Proponents and opponents would compete with each other to pursue the truth, and both parties would freely present their results, which should lead to great progress. The Maebashi Medical Association produced such an achievement mainly because the Gunma Medical Association had two viewpoints anyway.

At any rate, research group members of the Maebashi Medical Association are enthusiastic and still have regular study meetings at 7:30 p.m. Unlike labor unions, medical associations are organizations that are essentially academic and conduct some projects. Medical associations have the principle of modifying those projects to accommodate a new truth if revealed. I sympathized with research group members in principle and thus did my utmost to help them.

Taro Takemi, the president of the Japan Medical Association, was one of persons I respected partly because I conducted research at the School of Medicine, Keio University. It was customary for him to deliver an annual speech at the auditorium of the School of Medicine on New Year's Day, and I enjoyed listening to his clear-cut speech. I respected him because his actions were always based on reasonable grounds.

It should be remembered that Toyota gave grants. Blood sampling from 600 persons for five years is easy to say but difficult to perform; it is almost impossible. The well-known, reliable Toyota Foundation grant program allowed us to inform our stakeholders (such as school principals, homeroom teachers, parents, and city officials) that the survey by the Maebashi Medical Association was legitimate and facilitated our survey throughout the survey period. We greatly benefited from it. I was a judge when the research group of the Maebashi Medical Association applied for a grant at the second research contest titled "Looking at Your Surrounding Environment". Judges were chosen from different departments. I was the only physician, and it was difficult for other judges to understand influenza vaccines. I coercively persuaded them to select the rejected project as a rank B project (I failed to persuade them to select is as a rank A project). Receiving a grant from the Toyota Foundation (even a rank B) was something like public authorization or winning strong backing. Come to think of it, I am proud to say that the Maebashi Medical Association has produced particularly outstanding results among those of many projects supported by the Toyota Foundation grant program. Here, I gratefully acknowledge the Toyota Foundation.

In the research group consisting of practitioners who were not experts in basic medicine, it was difficult to conduct a statistical survey. Thus, the research group invited collaborators, including me, to compensate for the weakness as needed. In addition, the prevention section chief of the Maebashi Health Center and the school health section chief of the prefectural board of education were also invited to implement the survey.

For example, I presented the results of the influenza B infection and epidemics at the Japanese Society for Virology in Fukuoka and at the Japanese Society of Public Health in Sendai in October and November of the previous year. The presentations are outlined below. The school absentee rate was used to determine the epidemic period at each school, and absentees with influenza were identified to evaluate the vaccine efficacy. The results showed weak vaccine efficacy. However, this procedure showed no substantial difference in the infection rate at elementary and junior high schools between vaccinated areas and non-vaccinated areas (Maebashi City and Usui-gun).

Influenza B infection was compared. During discontinuation of vaccinations for six years or more, children were exposed to two or three epidemics of influenza B. I showed that each epidemic conferred immunity and explained that children acquired immunity similar to that obtained by vaccinations. Discontinuation of vaccinations naturally increased the number of patients. After six years of discontinuation, however, the number of patients in non-vaccinated areas was similar to that in vaccinated areas. I stressed that protection of high-risk individuals should be considered regardless of the validity of mass vaccinations because epidemics cannot be prevented simply by vaccinations of elementary and junior high school students, a group of population that accounts for only one-seventh of the total population.

At that time, the results of surveys conducted by the prefectural board of education and Gunma Institute of Public Health were used. Statistical data on excess mortality were generated by the Institute of Public Health, not the Maebashi Medical Association. However, we gave first priority to the pursuit of truth, made the best use of study groups, and developed a cooperative framework to make use of whatever was available.

Those details were studied by individual groups, in which they probably made different efforts and faced different difficulties. Still, they remained enthusiastic and discontinued vaccinations for five years or more, which resulted in a world-class field in terms of the scale. The valuable field will be used to produce a variety of results in influenza research in the future.

This compilation should be considered an interim report, and other data will be presented in due time. I hope the Toyota Foundation and many other persons will increase their understanding.

Regardless of this report, some may believe in vaccine efficacy and follow the conventional vaccination policy for fear of an increase in the number of patients after discontinuation, and other may discontinue vaccinations in the belief that long-term discontinuation produces results similar to that of annual vaccinations. At this point, my greatest concern is the need for a policy that allows voluntary vaccinations of high-risk individuals in this progressively aging society. Mass vaccinations of schoolchildren should be provided to protect children against infection (individual protection theory), not to prevent epidemics. From now on, efforts should be made to develop potent live or inactivated vaccines and investigate the dosing regimen. High-risk individuals, particularly bedridden older individuals, often show immunodeficiency. For protection of these older individuals, appropriate live vaccines or chemical formulations should be developed because administration of inactivated vaccines is unlikely to induce antibody production.

Our future challenges may include infection of high-risk individuals with influenza, epidemiology of influenza in adults, and implication of carriers of HI antibodies. Specifically, the involvement of adults in amplification of epidemics should be elucidated. Viruses are isolated from individuals with high HI antibody titers, and it should be determined whether vaccine with a symptom-relieving effect suppresses viral growth in the mucosa. At any rate, I hope the research group with a valuable field will continue the research enthusiastically.

VII. List of Group Members

Shuzo Yugami*	Maebashi Medical Association vaccination committee
Hideaki Yagi	Vice president of the Maebashi Medical Association
Yoshiichi Kanazawa	Maebashi Medical Association vaccination committee
Yuji Tokutsu	Director of the Maebashi Medical Association
Kazuyuki Kajita	Director of the Gunma Medical Association
Toichi Takahashi	Maebashi Medical Association vaccination committee (former chairperson)
Yoshiaki Tanaka	Maebashi Medical Association vaccination committee
Shigeo Kuwashima	Maebashi Medical Association vaccination committee (former chairperson)
Tatsuo Matsuyama	Maebashi Medical Association vaccination committee
Masako Suzuki	Maebashi Medical Association vaccination committee, school physician of the Aramaki Elementary School
Masumitsu Nakata***	Chairperson of the Maebashi Medical Association vaccination committee, school physician of the Ootone Elementary School
Takeshi Yamada	Maebashi Medical Association vaccination committee
Shigeki Nakajima**	Director of the Maebashi Medical Association
Yasushi Urano	Director of the Maebashi Medical Association, school physician of the Shikishima Elementary School
Fumihiko Fukazawa	School physician of the Shikishima Elementary School
Hiroshi Saito	School physician of the Aramaki Elementary School
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Toshiya Nomachi	School physician of the Katsuyama Elementary School
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Susumu Shigehara***	Vice manager of the Epidemiological Information Division, Gunma Institute of Public Health
Yasue Takeuchi	Manager of the Influenza Division, National Institute of Infectious Diseases
Kazumasa Oda	Director of the Virus Department, Kanagawa Institute of Public Health
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Mariko Fujita	Chief of the Prevention Section, Maebashi Health Center
Ikuo Hanyuu	Chief of the School Health Section, Gunma Prefectural Board of Education
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Shizue Abe	Former principal of the Shikishima Elementary School
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Takao Watanuki	Principal of the Katsuyama Elementary School
Fujio Morimura	Former principal of the Aramaki Elementary School, current principal of the Amagawa Elementary School
Reijiro Takebuchi	Principal of the Aramaki Elementary School
Seiju Kanbara	Former principal of the Ootone Elementary School, current principal of the Japanese School of Amsterdam
Fumio Nakayama	Principal of the Ootone Elementary School
Fumiko Sasamura	Former principal of the Utsuboi Elementary School
Kanekichi Yoshida	Former principal of the Utsuboi Elementary School, current principal of the Motosouja Elementary School
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Kaoru Imai	Former nursing teacher of the Shikishima Elementary School, current nursing teacher of the Dairoku Junior High School
Michiko Funato	Former nursing teacher of the Shikishima Elementary School
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Fusako Nakajima	Supervisor, Prevention Division, Health and Hygiene Section, Department of Environmental Services, Maebashi City
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Hajime Sugano	Supervisor, Prevention Division, Health and Hygiene Section, Department of Environmental Services, Maebashi City
Mariko Sugawa	Supervisor, Prevention Division, Health and Hygiene Section, Department of Environmental Services, Maebashi City
Hideyuki Suzuki	Manager, Prevention Division, Health and Hygiene Section, Department of Environmental Services, Maebashi City
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Susumu Fukazawa — Secretariat of the Maebashi Medical Association
Takuya Hoshino — Secretariat of the Maebashi Medical Association

* Director
** Responsible board member of the Maebashi Medical Association
*** Editorial committee

Postscript

I am very pleased that the report on influenza epidemics in a non-vaccinated area has been issued through five years of efforts and cooperation by members of the research group for the study of influenza. I believe that this unprecedented report in Japan will contribute much to the control of epidemics of influenza, a plague that is a final challenge to humans.

First, I wish to thank Akira Oya, director of the Virus Rickettsia Division, National Institute of Infectious Diseases and Munehiro Hirayama, professor at the University of Tokyo, for providing many suggestions and instructions on this survey after formation of the research group. I would like to express my respect and thanks to many participants in this survey, particularly the children and their parents at the five designated schools who cooperated on blood sampling for antibody titer testing for five years. I would like to express my gratitude to the collaborators in this survey, including principals and nursing teachers at elementary and junior high schools in the city, school health officials, and members of the Maebashi Municipal Board of Education.

In addition, I would like to extend my appreciation to the Gunma Institute of Public Health, the Maebashi Health Center, the School Health Section of the Gunma Prefectural Board of Education, the Gunma Medical Association, and the Gunma Prefecture Public Health Association for their cooperation in this survey. I gratefully acknowledge Seiichi Fujii, mayor of Maebashi, who recognized the importance of suggestions by the Maebashi Medical Association, decided to discontinue mass influenza vaccination, and cooperated in subsequent research group activities.

Among the members of the Maebashi Medical Association, I would like to thank the school physicians for their cooperation in this survey. I would also like to thank Yutaka Yamashita, then president of the Maebashi Medical Association who made a significant decision to stop mass vaccinations, as well as Hideaki Yagi (current vice-president) and Yoshiichi Kanazawa who were responsible board members at that time and made efforts behind the scenes to form and manage the research group smoothly. I asked Susumu Fukazawa and Takuya Hoshino, who are secretariats of the research group, for cooperation in editing and proofreading this report. Without their cooperation, this report would not have been completed. I appreciate their efforts.

Finally, the Toyota Foundation provided substantial support for this survey. This survey benefited greatly from its long-term support, from the research contest grant program to research grants, and research outcome presentation grants. I would like to express my deep and sincere gratitude.

Shigeki Nakajima
Responsible board member of the Maebashi Medical Association

Editorial note

This document is an English version of "Influenza Epidemics in a Non-Vaccinated Area" (Maebashi Research Group for the Study of Influenza Epidemics, director: Shuzo Yugami, Toyota Foundation Grant Research Report, published in 1987). Though there have been requests for the English version since the original version was published, the requests did not materialize because no appropriate person or financial help was available. Recently a plan to publish an English translation was presented to the Maebashi Medical Association by a citizens' group, which triggered the holding of a meeting of the members of the Medical Association (research group members of that time) to discuss the plan. They considered the part of the report played in the influenza vaccine administration of that time, the social impact, and the existing value as a document, and decided to publish it as archival material by the Maebashi Medical Association.

It was decided that the Maebashi Medical Association's fund for healthcare and cultural contributions (Yugami Fund) would cover the publishing costs with the approval of the Maebashi Medical Association. The English translation was commissioned as a cooperative project. We deeply appreciate the contributions of Professor Hirokazu Arakawa, Assistant Professor Toshio Watanabe, and the many staff members at the Department of Pediatrics, Gunma University Graduate school of Medicine, for the proofreading. Also, we sincerely thank Mr. Takuya Hoshino, the Secretariat of the Maebashi Medical Association, who invested his energy in editing.

The basic policy for an English translation was to stay true to the original document. Except for corrections of some errors in Figure 6 in the original document in accordance with the table, the changes were limited to corrections of obvious errors in the writing of words and numbers and modifications of simpler expressions. There was no change in the contents or conclusions.

We sincerely thank all the persons cooperatively involved in making the English version and at the same time deeply apologize for the delay in the completion of the English version. Unfortunately, the research group director Shuzo Yugami passed away in August 1997. The project would have developed differently if he were alive. We cordially dedicate this document to him. The Maebashi Research Group for the Study of Influenza Epidemics was reorganized in 1995 and now exists as the Maebashi Research Group for the Study of Infectious Diseases.

(Author: Masumitsu Nakata)

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