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○ Yoshio Hirota. Ecological fallacy and scepticism about influenza vaccine efficacy in Japan: The Maebashi Study. Vaccine 26 (2008) 6473-6476

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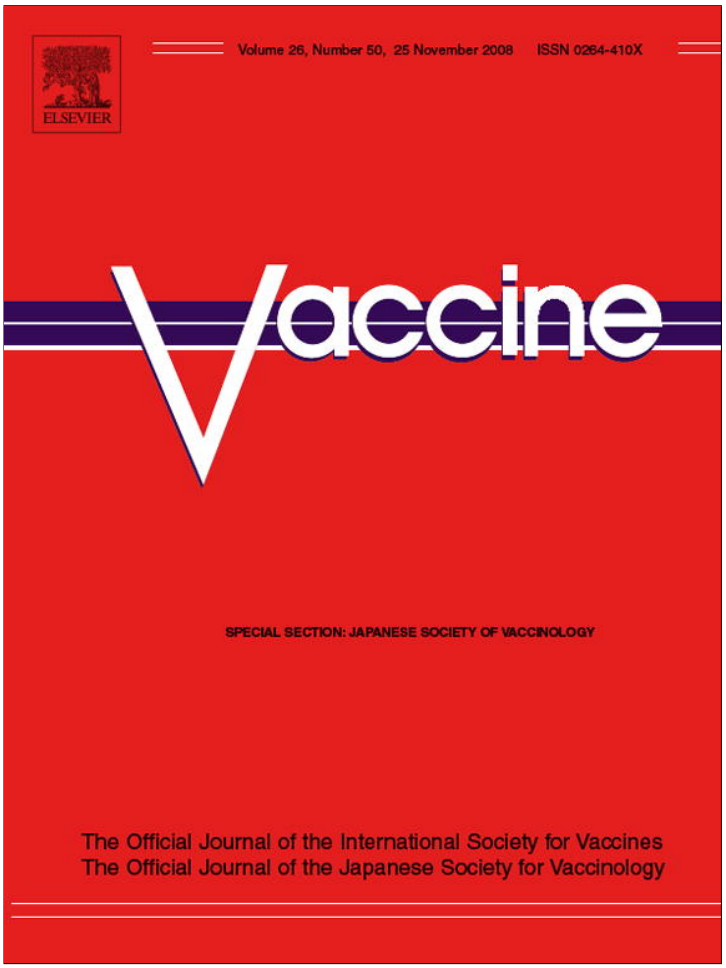

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History of influenza vaccination programs in Japan

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ABSTRACT

In 1976, influenza mass vaccination among schoolchildren was started under the Preventive Vaccination Law, which was intended to control epidemics in the community. However, in the late 1980s, questions about this policy and vaccine efficacy arose, and a campaign against vaccination began. In 1994, influenza was excluded from the target diseases list in the Preventive Vaccination Law, without considering the immunization policy with respect to the common indications in high-risk groups. In 2001, the Law was again amended, specifying target groups, such as the elderly aged 65 or over, for influenza vaccination. In the 2005–2006 season, vaccine coverage among the elderly reached 52%. This shows that the need for vaccination has gradually become understood. However, the anti-vaccination campaign, which claims that the influenza vaccine has no efficacy, is still active. Vaccine efficacy studies that were not properly conducted are also being reported. In 2002, the Ministry of Health, Labor, and Welfare organized a research group on vaccine efficacy consisting of epidemiologists. The present symposium, as part of the 9th Annual Meeting of the Japanese Society for Vaccinology in 2005, was planned to further introduce epidemiological concepts useful in studying influenza vaccine efficacy.

1. Introduction

Japan is the only country in the world to have adopted mass vaccination of schoolchildren for influenza control, which resulted in an anti-vaccination campaign that still continues and claims that influenza vaccine has no efficacy. This has resulted in two peculiar circumstances in Japan. First, many people are concerned about influenza vaccine efficacy, whether or not they have the specialized knowledge required to understand the issue. Second, self-proclaimed specialists, who often lack specialized knowledge, nevertheless consider themselves specialists. As a result, people interested in influenza vaccine efficacy hear contradictory comments from real specialists, would-be specialists, and lay people, with lay people having the loudest voice.

The present symposium was planned to summarize the essential knowledge needed to understand the issues involved in influenza vaccine efficacy. Here, as a prologue to the symposium, we will briefly review the history of influenza vaccination programs in Japan, so that international readers can appreciate how lack of knowledge has contributed to difficulties in program implementation.

2. The beginning of influenza mass vaccination

In Japan, the Preventive Vaccination Law was promulgated in 1948, although influenza was not listed at that time. After the great impact of the 1957 Asian flu pandemic, a special program to promote influenza vaccination among schoolchildren was started in 1962, though it was not mandated by the Law. After the 1968 Hong Kong flu pandemic, the government was determined to establish further effective countermeasures against influenza. However, the rationale behind influenza control, which is to prevent severe complications and death among high-risk individuals, was not reflected in the vaccination strategy, and schoolchildren continued to be the sole target of active influenza vaccination. This somewhat one-sided policy gradually became entrenched, and studies that supported the approach were emphasized [1]. In 1976, the Preventive Vaccination Law was amended to include influenza among the target diseases, and mass vaccination of schoolchildren was started. This policy was intended to control influenza epidemics in the entire community by suppressing transmission in schools, while in Western countries, on the other hand, influenza vaccine was being given mainly to high-risk individuals, such as the elderly, at that time [2]. This was the beginning of chaos in influenza vaccination policy and in the influenza vaccine efficacy

Abbreviations: CI, confidence interval; MHW, Ministry of Health and Welfare; MHLW, Ministry of Health, Labor, and Welfare.

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debate that took place during the following 20 or more years in Japan.

3. Effect of mass vaccination on influenza impact

The unconventional policy of mass vaccination of schoolchildren attracted attention about whether it could actually mitigate the impact of influenza. However, no positive result of the policy was clearly shown [3]. A recent study reported that mass vaccination of schoolchildren reduced influenza mortality among the elderly; excess deaths among the elderly were lower during mass vaccination and then increased after discontinuation of the program [4]. However, this finding was criticized from several perspectives, including the increase in the elderly population, the rapid increase in the number of nursing homes and other living centers for seniors, and the definition of the influenza season [5]. Another study inferred that the discontinuation of mass vaccination among schoolchildren was responsible for an increase in influenza-associated deaths among young children [6]. On the other hand, a study focusing on the elderly in the United States failed to correlate increased vaccine coverage with a decline in mortality in any age groups [7]. In any case, these studies, whether the results were positive or negative, cannot provide solid evidence for influenza vaccine efficacy both at the population level and at an individual level, because they are "ecological studies." The subtlety involved in interpreting such studies has been discussed elsewhere [8].

4. Scepticism about influenza vaccine efficacy

From 1976 to 1987, more than 10 million schoolchildren annually received influenza vaccine, with the peak of 16.5 million vaccinees in each of 1983 and 1984. However, seasonal epidemics continued to occur, the elimination of which had been the objective of the mass vaccination policy. Furthermore, in Japan, individuals use the term "Kaze" (meaning cold) almost interchangeably with flu, and would say "I contracted Kaze, even though I received an influenza vaccine" [9]. School physicians, who were mostly private community practitioners who were in charge of school mass vaccination, were often asked about influenza vaccine efficacy by parents and teachers. This was an unexpected question for these frontline clinicians, since they had seldom been queried about the other vaccines. Many of them decided to study influenza vaccine efficacy by comparing the frequencies of Kaze, severe Kaze, or absenteeism due to Kaze between vaccinees and non-vaccinees in the school setting. Many such studies failed to detect vaccine efficacy due to misclassification of disease; however, they played an important role in stigmatizing influenza vaccine. Thus, in the late 1980s, two issues arose: whether influenza mass vaccination effectively prevents community epidemics; and whether influenza vaccine effectively prevents influenza attacks in individuals. With the blending of these two questions by the campaign against influenza vaccination, which involved the mass media, teachers' union, consumers' union, and other groups, influenza vaccine coverage among schoolchildren declined steeply from about 80% at its peak to 18% in 1992.

5. Discontinuation of mass vaccination programs

In contrast to the many reports that alleged that influenza vaccine had little or no efficacy, three quality Japanese studies were also published. The first one, a randomized, controlled study, was done among high school students during the 1968–1969 season. This study demonstrated that vaccine efficacy against serologically confirmed infection was 80% ($P < 0.001$) for A(H3) and 43% ($P < 0.01$) for B [10]. The second study, a case–control study among elementary schoolchildren, was done during the 1988–1989 season when A(H1) viruses were predominant. After adjusting for several confounders, the odds ratio of vaccination against influenza-like illness with fever $\geq 39\,^{\circ}C$ was calculated to be 0.33 (95% confidence interval (CI): 0.14–0.78) [11]; of interest, this finding was wrongly cited in a recent systematic review article [12]. The third study, an observational follow-up study among asthmatic children aged 2–14 years in the clinic setting, showed that vaccine efficacy against infection was 67.5% ($P < 0.01$) for A(H3), 43.7% ($P < 0.01$) for B, and 42.1% ($P < 0.01$) for both A(H3) and B combined [13]. However, these scientific reports were not considered when the vaccination program was being evaluated, since the vaccination policy and vaccine efficacy were being studied and discussed mainly by pediatric practitioners, who had an interest in school health, and by microbiologists, who were interested in the vaccine. In June 1994, the Preventive Vaccination Law was amended to exclude influenza from the list of target diseases without considering an immunization policy that would be based on the common indications for high-risk groups. Thus, influenza mass vaccination among schoolchildren that had lasted for nearly 20 years under the Law was discontinued. This is in striking contrast to what happened in the United States, where, in 1993, the federal government's Medicare program started reimbursement for the cost of influenza vaccine and its administration.

6. The pendulum swings back

At a time when interest in influenza disease and the influenza vaccine was extraordinarily low, several authors reviewed the misunderstandings about the vaccine and vaccination strategy [9,14]. Then, in 1997, the first Committee for Influenza Pandemic Preparedness was established by the Ministry of Health and Welfare (MHW) and clearly specified the rationale of influenza control and influenza vaccine efficacy, given the results of the three abovementioned studies [10,11,13]. The committee also reviewed the frequency of influenza vaccine side effects, which had been officially recognized and compensated for during the mass vaccination era (1977–1994): 116 events among 329,339,615 vaccinations, that is "0.35×10^{-6} (95% CI: 0.29×10^{-6} to 0.42×10^{-6}) per vaccination", which can also be stated as "0.07×10^{-6} per week after vaccination", assuming that the maximum duration between vaccination and the onset of side effects is 35 days. Once again, the mass media began to show their interest in influenza, and newspapers headlined influenza deaths in nursing homes. Thus, it appeared as if the pendulum were swinging back, though the negative view of influenza vaccine persisted. At that time, there was an article published in a magazine alleging that the group of people with favorable views towards influenza vaccine had been the result of collaboration among vaccine manufactures, scientifically biased researchers, and the MHW [15]. It also presented survey data on influenza attack rates (vaccinees 71.0%, non-vaccinees 75.4%) and absenteeism due to influenza (vaccinees 73.3%, non-vaccinees 72.8%) and concluded that it would be hard to accept that influenza vaccine is effective. Fortunately, unlike the period from the late 1980s to the early 1990s, few people agreed with this view, but unfortunately, there were still only a few individuals who could instantly understand the drawbacks of such data reported in the magazine. It is quite clear that the survey data reported suffered substantially from misclassification of disease due to loose criteria, such as "Kaze", particularly when compared to the reported attack rates (45–60%) among schoolchildren during the 1957 Asian flu pandemic.

7. A new vaccination strategy and the present status

During the 1996–1997 influenza season, the MHW issued a notice to all prefecture governments that welfare institutes were to make the necessary arrangements to ensure that all residents could receive influenza vaccine. In 1999, the MHW and the Japan Medical Association collaborated on a campaign whose slogan was, "Don't confuse influenza with Kaze. Don't underrate influenza." Finally, in 2001, the Preventive Vaccination Law was amended to again include influenza, specifying two target groups: the elderly aged 65 or older and those aged 60–64 years with heart, kidney, lung, and other chronic disorders. Under this Law, more than 99% of eligible persons are elderly, since the 60–64-year-old age group is normally classified as the disabled people who are officially registered for special welfare services. Under the Law, municipalities have to take responsibility for offering vaccinations to the target groups. The cost of providing the influenza vaccine, including not only the cost of the vaccine and the cost of its administration, but also a health consultation fee to determine whether it is indicated, is roughly 5000 Japanese Yen (¥); the municipality provides a subsidy (¥4000), and the individual contributes a self-payment (¥1000). The cost and the division of the cost are not equal among the municipalities, but they depend on the agreement between the municipal government and the community medical association. The relatively high cost of vaccination reflects the need to deal with the negative perception of influenza vaccine safety, since the anti-vaccination campaign always exaggerates the side effects of the vaccine.

Since 2001, vaccine coverage among the target population has been consistently increasing: 28% in 2001–2002, 35% in 2002–2003, 45% in 2003–2004, 47% in 2004–2005, and 52% in the 2005–2006 season. These figures reflect the coverage among the elderly aged 65 or over, since they account for almost all of the target population. Thus, the significant health impact of influenza and the important role that vaccination plays have gradually become understood by the general public. Geriatric hospital physicians have played an important role in disseminating information about influenza vaccine efficacy. They closely observe each patient throughout the influenza season, since influenza-related complications, such as pneumonia, are critical issues in their hospitals. They can, therefore, themselves observe the reduction in severe complications and death among vaccinated patients compared to non-vaccinated patients. This situation is quite different from that of the school physicians who were previously engaged in mass vaccination; they only had contact with the children who visited their clinics during influenza season. Many or almost all such children suffering from flu symptoms had received influenza vaccine due to the high vaccine coverage rates that had been achieved with the mass vaccination programs.

8. Recent developments surrounding influenza vaccine

In Japan, while anti-vaccination campaigns are still active, they have weakened and have some peculiar features. The opposition is based upon the view that influenza vaccine has a little or no efficacy but a high risk of side effects, and that influenza is not a serious disease for which preventive intervention is required. It is really regrettable that there are physicians who inexplicably share the views of the anti-vaccination activists and object to influenza vaccination. This situation is in sharp contrast with that in Western countries where the major reasons for refusing vaccination are typically religious beliefs or personal principles.

Many physicians and pediatricians still feel frustrated by the degree of efficacy of the present influenza vaccine. They usually make apologies when administering influenza vaccine, explaining that "Every vaccine recipient cannot necessarily avoid contracting influenza." To resolve this dilemma, they perform their own studies of vaccine efficacy. They believe that the failure to detect vaccine efficacy during the mass vaccination era was solely due to the use of a clinically defined outcome. Now, they are confident that laboratory-confirmed influenza can be identified in their clinics using a newly developed commercial rapid diagnostic kit. Thus, they tend to first register vaccinated and non-vaccinated subjects before the influenza season, and then simply calculate the proportion of clinic visitors with positive rapid antigen tests among the initially enrolled subjects by vaccination status; they do not include any information on non-clinic visitors. It appears difficult for frontline clinicians to recognize that observing individual study subjects with equal intensity is of paramount importance in these types of studies. As in the 1980s, although fewer in number, several studies have been conducted by clinicians who lack even a rudimentary appreciation of epidemiologic principles, including selection bias, confounding, and misclassification. Of even greater concern is that there are few Japanese researchers who can critically review such flawed studies, which results in the presentation at scientific meeting or publication in journals of fundamentally flawed studies [16].

Thus, in 2002–2004, the Ministry of Health, Labor, and Welfare (MHLW: the former MHW was reorganized in 2001) created a research group consisting of epidemiologists, for the "Appraisal of influenza vaccine efficacy and vaccination policy in conformity with evidence-based medicine", and granted them a total of ¥99,750,000. This was the first research group created by the MHLW that focused on the epidemiological aspects of influenza vaccine. The formation of this group attracted the attention of epidemiologists to influenza vaccine. Most of the epidemiologists had never considered that vaccine research was a field in which they could be involved. It is also undeniable that pediatricians and microbiologists had considered influenza vaccine to be their own exclusive research area and felt reluctant to work with epidemiologists. Several epidemiologists in the research group took a great interest in the field and have successfully conducted studies of vaccine efficacy [17–20].

Following the success of the first research group, in 2005–2007, the MHLW set up a successor group for "Analytical epidemiologic study on the effectiveness of influenza and other vaccines and vaccination policy" and has already granted ¥94,900,000 for the first 2 years. In this second research group, the epidemiologists who gained experience doing influenza research in the first group are expected to expand their investigations in close cooperation with pediatricians, physicians, and microbiologists, as well as to transfer their epidemiological knowledge and skills to their co-researchers. Thus, as a result of the common perception of the vaccine efficacy study, the present symposium on influenza vaccine from the epidemiological viewpoint was held at the 9th Annual Meeting of the Japanese Society for Vaccinology in Osaka on October 15–16, 2005. The following articles dealing with the topics covered at the symposium were collected to serve as the basis to convey the essential knowledge of epidemiology, to review the prior studies for use as a reference, and to present community-based studies recently carried out by epidemiologists with the cooperation of clinicians and virologists.

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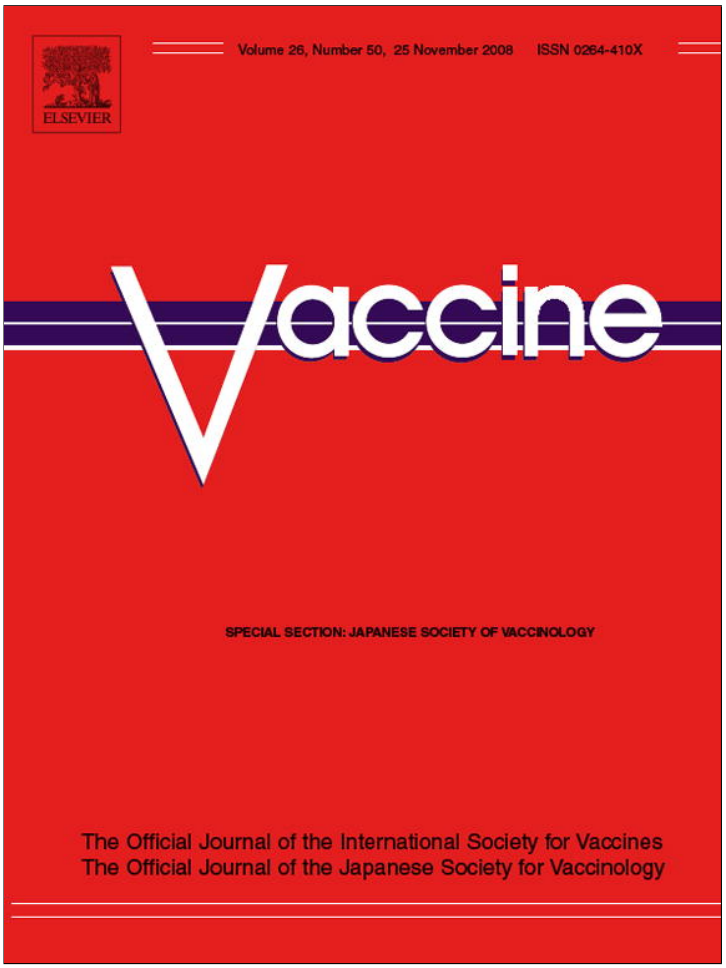

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Ecological fallacy and scepticism about influenza vaccine efficacy in Japan: The Maebashi Study

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ABSTRACT

In 1979, Maebashi City discontinued influenza mass vaccination immediately after a case of vaccine-related convulsion occurred. A research group of the Maebashi City Medical Association studied the effects of mass vaccination on influenza activity in two cities without mass vaccination programs and three cities with mass vaccination programs (Maebashi Study). Due to possible issues of validity arising from the non-randomized design of the study, the authors of the Maebashi Study reserved discussion on the vaccine efficacy that they calculated from the attack rates among the non-vaccinees and vaccinees. Instead, they compared the overall attack rates in Maebashi and among the twice-vaccinees in the cities with mass vaccination programs. The authors limited their discussion to the fact that influenza activity in Maebashi was not materially different from that in cities with mass vaccination programs. Anti-vaccination activists misconstrued this to mean that the absence of a correlation between attack rate and vaccine coverage implies that influenza vaccine has no efficacy. This is a good example of the "ecological fallacy", which refers to the fact that a relationship between two variables at the population level does not necessarily imply the same relationship at an individual level.

1. Introduction

It has been said that one report played a decisive role in instilling scepticism about influenza vaccine efficacy in Japanese society. The study, known as the "Maebashi Study", was performed by a research group organized by the Maebashi City Medical Association and was conducted primarily between 1981 and 1986.

The Maebashi Study is almost always cited by anti-vaccination activists, as well as by medical professionals, as evidence that influenza vaccination is not effective. During the 1979–1980 season, Maebashi City discontinued its influenza mass vaccination program for school children when a case of severe convulsion occurred in a child after the first dose; the second dose inoculation program was cancelled that season. Subsequently, the Medical Association investigated influenza vaccine efficacy. The results of the study were published in 1987, in a report entitled "Influenza Epidemics in a Non-vaccinated Area" [1]. However, it is important to note that most influenza specialists have never read this report; they simply believe that, based on mass media reports, the Maebashi Study demonstrated that influenza vaccine had little or no efficacy.

In the preface to the report, the authors stated the background and aim of their study as follows:

> "...We have no intention of fully investigating the protective effect of influenza vaccine against infection or attack. However, we are greatly concerned with whether vaccination of pupils and students would provide any protection against an influenza epidemic. Now is the time to review the compulsory mass vaccination program for these age groups."

Thus, it is clear that the aim of the Maebashi Study was to investigate the effect of mass vaccination on influenza activity in the community, as shown by the title of the report "Influenza Epidemics in a Non-vaccinated Area."

2. An outline of the Maebashi Study

2.1. Subjects and methods

Most of the study was done during the 1984–1985 season, which had a type B virus epidemic, and during the 1985–1986 season, when A(H3) viruses were circulating. The attack rate in all school children was investigated in five selected cities in the Gunma Prefecture: Maebashi and Annaka, which had discontinued mass vaccination; Takasaki, Kiryu, and Isesaki, which were still continuing mass vaccination. Information on influenza attacks was

Abbreviation: ILI, influenza-like illness.

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retrospectively collected from more than 99% of the subjects. An influenza-like illness (ILI) was defined as "fever ≧ 37 °C plus absenteeism ≧ 2 consecutive days" or "absenteeism ≧ 3 consecutive days" during an influenza outbreak in the appropriate school. An outbreak was characterized as the period during which the proportion of absenteeism due to influenza symptoms among school children was 2% or more.

The authors again emphasized in the beginning of this section that:

> ". . .The vaccine effectiveness we discuss hereafter indicates the one relevant to the group of people, not to the individuals."

2.2. Results and discussions

The main results of the Maebashi study are shown in Tables 1 and 2.

First (noted by superscript "b" in the Table), the authors pooled the data for the three cities that were still continuing with mass vaccination and calculated the attack rate as a whole for the 1984–1985 season (Table 1); it was 54.7% (3962/7241) among non-vaccinees and 40.6% (13,255/32,641) among twice-vaccinees, for an estimated effectiveness of twice-vaccination of 25.8% [(54.7–40.6)/54.7]. The corresponding attack rates for the 1985–1986 season (Table 2) were 33.3% (2564/7702) among non-vaccinees and 20.3% (5729/28,207) among twice-vaccinees, for a vaccine effectiveness of 39.0% [(33.3–20.3)/33.3]. At this point, the authors recognized that the non-randomized study design could have introduced a validity problem. They suggested that asthmatic children, who usually account for about 5% of Japanese school children, were likely not vaccinated; of note, the Japanese vaccination guideline includes asthma as well as egg allergy as conditions that require special attention if influenza vaccine is to be given. The authors also believed that children in poor health might not have been vaccinated if they had symptoms at the time that the vaccine was being given. Thus, the non-vaccinated group was thought to include more subjects that were prone to develop influenza symptoms, which would have led to vaccine effectiveness being overestimated. Thus, the authors undertook additional analyses.

Second (noted by superscript "a" in the Table), the authors regarded the overall attack rate in Maebashi city as the reference rate (non-vaccinated area), and compared it with the attack rate among all twice-vaccinees in the three cities that continued their mass vaccination programs (vaccinated area). In the 1984–1985 season (Table 1), the comparison of the attack rates between the non-vaccinated (42.8%) and vaccinated areas (40.6%) showed that vaccination program was associated with an absolute risk reduction of 2.2% points, with a prevented fraction of 5% (calculated in the same way as ordinary vaccine efficacy). In the 1985–1986 season (Table 2), comparison of the two attack rates (27.7% vs. 20.3%) demonstrated an absolute risk reduction of 7.4% points, with a prevented fraction of 2.7%. Thus, the vaccination program appeared to have only a limited effect.

3. Interpretation by the research group

When interpreting the results of their first analysis, the authors emphasized that the groups had an imbalance of characteristics, though they did not use the term "confounding." Had a more complete epidemiological analysis been done, it would have adjusted for the confounding effects, using the information on potential confounders collected initially. Of note, it should be emphasized that, even 20 years after the Maebashi Study, the issue of confounding is not often adequately addressed in vaccine efficacy studies done by Japanese clinicians.

With respect to the study's second analysis, it seems unlikely that attack rates in the non-vaccinated and vaccinated areas were sufficiently comparable, since influenza activity is a phenomenon that is time- and place-specific. In addition, the unit of observation was changed from individuals in the first analysis to groups in the second analysis. Had the authors contrasted the overall attack rate between the non-vaccinated and vaccinated areas, as would be done in an ordinary ecological study, they would have noticed that their analysis was illogical, given that the comparison showed that the vaccination program had a negative effect (Table 1): a 42.8% attack rate in Maebashi and a 43.7% attack rate in the three cities that were grouped together as the vaccinated area during the 1984–1985 season.

The authors avoided discussing vaccine efficacy at the individual level, as they mentioned in the preface to the report and in the beginning of the main chapter. Based upon the slight effect of the vaccination program shown in their second analysis, they concluded:

> ". . .Influenza activity in Maebashi in non-vaccinated areas did not show any material difference from that in vaccinated areas. We therefore believe that the idea of preventing an influenza epidemic in the community by using school children as a breakwater has been proven a complete failure."

Thus, the authors interpreted their study's results carefully, recognized that it had some limitations, and never deviated from scientifically sound principles in explaining influenza vaccine efficacy.

4. Ecological fallacy drawn from the Maebashi Study

Anti-vaccination activists incorrectly cite the Maebashi Study in their campaign and have put the following statement on their website:

> ". . .The doctors of the Maebashi City Medical Association . . . thoroughly surveyed absenteeism and illness attack rates in the vaccinated and non-vaccinated areas. This outstanding epidemiologic study comparing 45,000 school children in a vaccinated area with 25,000 school children in a non-vaccinated area revealed that influenza vaccine cannot prevent epidemics, not only in the community but also among children, and the efficacy of vaccine was thus negated."

> ". . .As shown by the data of the 1984–1985 season with type-B virus circulation, . . . vaccine coverage was 0.1% in Maebashi as compared to 91.5% in Takasaki, but the actual incidence was nearly the same, 42.8% and 40.1%, respectively. The situation was similar in cities other than Takasaki. These data demonstrate good reasons for concluding that influenza vaccine has no efficacy."

In their statements, the activist group compared the attack rate in relation to the vaccine coverage; the unit of observation was each city, not the individual, although the original data had included information on each individual subject. To assert that influenza vaccine had no efficacy provides a good example of the "ecological fallacy." On the other hand, the authors of the Maebashi Study carefully focused their discussion on the effect of mass vaccination programs.

5. Consideration

The Maebashi Study group conducted a large-scale survey, though there were some limitations. They must be respected for the enormous effort they made to conduct the study and for their pru-

Table 1
Influenza vaccination and attack rates of influenza-like illness (ILI) among school children in the 1984–1985 season (Maebashi Study)

City	Vaccination	Number of subjects (distribution%)	Number of ILIs (attack rate%)
Cities with no mass vaccination			
Maebashi	Total	25,122 (100)	10,743 (42.8)[a]
	Non-vaccinees	25,101 (99.9)	10,738 (42.8)
	Once-vaccinees	18 (0.1)	5 (27.8)
	Twice-vaccinees	3 (0.0)	0 (0)
Annaka	Total	4,021 (100)	1,832 (45.6)
	Non-vaccinees	4,021 (100)	1,832 (45.6)
	Once-vaccinees	0 (0)	0 (0)
	Twice-vaccinees	0 (0)	0 (0)
Cities with mass vaccination			
Total	Total	45,336 (100)	19,817 (43.7)
	Non-vaccinees	7,241 (16.0)	3,962 (54.7)[b]
	Once-vaccinees	5,445 (12.0)	2,603 (47.8)
	Twice-vaccinees	32,641 (72.0)	13,255 (40.6)[a,b]
Takasaki	Total	22,119 (100)	8,865 (40.1)
	Non-vaccinees	1,887 (8.5)	1,017 (53.9)
	Once-vaccinees	1,291 (5.8)	597 (45.9)
	Twice-vaccinees	18,941 (85.6)	7,254 (38.3)
Kiryu	Total	12,374 (100)	5,324 (43.0)
	Non-vaccinees	2,751 (22.2)	1,425 (51.8)
	Once-vaccinees	2,318 (18.7)	1,039 (44.8)
	Twice-vaccinees	7,305 (59.0)	2,860 (39.2)
Isesaki	Total	10,843 (100)	5,628 (51.9)
	Non-vaccinees	2,603 (24.0)	1,520 (58.4)
	Once-vaccinees	1,836 (16.9)	967 (52.7)
	Twice-vaccinees	6,395 (59.0)	3,141 (49.1)

ILI: "fever ≧ 37 °C plus absenteeism ≧ 2 consecutive days" or "absenteeism ≧ 3 consecutive days." Observations from January 8, 1985 to February 28, 1985.
[a] Compared in the second analysis.
[b] Compared in the first analysis.

Table 2
Influenza vaccination and attack rates of influenza-like illness (ILI) among school children in the 1985–1986 season (Maebashi Study)

City	Vaccination	Number of subjects (distribution%)	Number of ILIs (attack rate%)
Cities with no mass vaccination			
Maebashi	Total	24,266 (100)	6,714 (27.7)[a]
	Non-vaccinees	24,249 (99.0)	6,709 (27.7)
	Once-vaccinees	10 (0.0)	5 (50.0)
	Twice-vaccinees	7 (0.0)	0 (0)
Annaka	Total	4,071 (100)	903 (22.2)
	Non-vaccinees	4,056 (99.6)	899 (22.2)
	Once-vaccinees	11 (0.3)	3 (27.3)
	Twice-vaccinees	4 (0.1)	1 (25.0)
Cities with mass vaccination			
Total	Total	43,687 (100)	10,513 (24.1)
	Non-vaccinees	7,702 (17.6)	2,564 (33.3)[b]
	Once-vaccinees	7,778 (17.8)	2,220 (28.5)
	Twice-vaccinees	28,207 (64.6)	5,729 (20.3)[a,b]
Takasaki	Total	21,381 (100)	4,481 (21.0)
	Non-vaccinees	2,063 (9.6)	637 (30.9)
	Once-vaccinees	2,106 (9.8)	640 (30.4)
	Twice-vaccinees	17,212 (80.5)	3,204 (18.6)
Kiryu	Total	11,657 (100)	2,933 (25.2)
	Non-vaccinees	2,628 (22.5)	846 (32.2)
	Once-vaccinees	3,470 (29.8)	817 (23.5)
	Twice-vaccinees	5,559 (47.7)	1,270 (22.8)
Isesaki	Total	10,649 (100)	3,099 (29.1)
	Non-vaccinees	3,011 (28.3)	1,081 (35.9)
	Once-vaccinees	2,202 (20.7)	763 (34.7)
	Twice-vaccinees	5,436 (51.0)	1,255 (23.1)

ILI: same as Table 1. Observations from November 3, 1985 to December 28, 1985.
[a] Compared in the second analysis.
[b] Compared in the first analysis.

dent attitude in interpreting the results. On the other hand, many so-called influenza specialists, who misunderstand the Maebashi Study based on the mass media information, simply believe that the study raised doubts about influenza vaccine efficacy. Needless to say, they have not delved into the details of the study itself, nor have they noticed its important message on case definition, confounding, selection bias, surveillance with equal intensity, among others.

The ecological fallacy that has been intentionally drawn from the data in the Maebashi Study has been spread by the anti-vaccination campaign. Currently, only a few influenza specialists can differentiate between inferences drawn from an ecological study and those drawn from ordinary, analytical epidemiological studies. Influenza specialists involved in vaccination programs should be expected to acquire such basic knowledge and to use it to correctly inform the general public about the propaganda against the influenza vaccine. Influenza specialists, both in Japan and in other countries, must understand the advantages and disadvantages of ecological studies, in the light of recent ecological studies and their impact [2,3].

References

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[3] A statement by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH); February 10, 2005. http://www.cdc.gov/flu/pdf/statementeldmortality.pdf.

2010 年 9 月 14 日

日経 BP 社日経メディカル編集部　北澤京子

（1） 対象となる疾病･ワクチンのあり方について

・集団の利益と個人の利益との関係について

予防接種法第一条は、公的関与の下に実施される予防接種は、接種を受けた個人にとっての利益に加えて、社会全体の利益（＝社会全体における疾病の発生、まん延の減少→公衆衛生の向上及び増進）に寄与するという目的があると読める（だからこそ、一類疾病は接種を受ける側にも努力義務が課せられている）のですが、こうした理解でよいのでしょうか。予防接種法におけるこのコンセプトと、いわゆる VPD のコンセプトは矛盾しないのでしょうか。

・ワクチンの経済評価は必要だが、その方法論や解釈の仕方はさらに議論を

かけられる公費が無尽蔵でない以上、疾病・ワクチンの追加（削除）の決定に際しては、有効性・安全性の評価に加えて、わが国における経済性の評価も必要だと思います（他の医療技術についても同様だが、わが国ではなされていない)。ただし経済評価の方法論、結果の信頼性/解釈の仕方、および政策決定に用いる際の妥当性については、さらに精査してほしいと思います（第 9 回部会資料 2-5)。

（5）予防接種に関する評価・検討組織のあり方について

・評価・検討組織においては、委員の利益相反（COI）を開示すべき

ワクチンの評価・検討組織において、各委員は関連業界との COI を開示すべきだと思います（第 9 回部会資料 2-5)。当然、本部会およびワクチン評価に関する小委員会、さらにその下の作業チームも同様の扱いとすべきです。米国 ACIP 等の海外の評価･検討機関でも COI への対応が取られており（第 12 回部会資料 3-1)、日本で開示しなくてよい理由はないと思います。

事務局から先日、「作業チームのメンバーに対しても（COI を自己）申告していただく方向で調整中」との連絡がありましたが、調整の結果についてご報告をお願いいたします。

・ワクチンの有効性は「患者/国民アウトカム」で評価してほしい

ワクチンは、承認段階では代用アウトカムで評価され、真のアウトカム（＝患者/国民アウトカム）は市販後に確認するしかないにもかかわらず、肝心の接種後の評価が不十分であるとの指摘がありました（第 7 回部会資料 2-2、2-7)。ワクチンの有効性の評価は、治療薬に比べて難しい点が多いことは理解できますが、「有効かどうか分からない」ワクチンの接種を国民に推奨することはできないと思います（第 9 回部会資料 2-5)。

例えば現在検討中の HPV ワクチンの場合、使用経験が短いため、女児へのワクチン接種が将来の子宮頸癌の罹患やそれによる死亡（＝患者/国民アウトカム）を本当に減らすのか、まだ実証されていません。ちなみに癌の予防対策として既に実施されている癌検診の有効性は、死亡率減少効果で評価されることが一般的です。HPV を含む新規のワクチンについて、患者/国民アウトカムで見た有効性が証明される以前に導入するという行政の判断はあり得ると思いますが、その場合でも並行して臨床研究や疫学研究を実施し、最終的に患者/国民アウトカムによる有効性評価ができる体制をつくってほしいと思います。

・ワクチンだけでなく、多様な手段の組み合わせ（ベスト･ミックス）を検討してほしい

対象疾患の予防手段として、ワクチン以外の方法（HPV ワクチンと子宮頸癌検診、インフルエンザワクチンと学級閉鎖など）が想定される場合は、ワクチン単独の評価に加えて、当該疾患による被害を最小にするためのベスト・ミックスを総合的に検討すべきだと思います。