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# Vaccine epidemiology: Its role in promoting sound immunization programs in Japan

Yoshio Hirota [a,b,*], Kotaro Ozasa [c], Takashi Nakano [d]

[a] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[b] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan
[c] Department of Epidemiology, Radiation Effects Research Foundation, 5-2, Hijiyama-koen, Minami-ku, Hiroshima 732-0815, Japan
[d] Department of Pediatrics, Kawasaki Medical School, 2-1-80, Nakasange, Kita-ku, Okayama 700-8505, Japan

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ABSTRACT

In Japan, the Vaccine Epidemiology Research Group created by the Ministry of Health, Labour and Welfare has played an important role in demonstrating the solid scientific basis for vaccine efficacy and safety since 2002. Members of the group, including epidemiologists, clinicians and microbiologists, have been conducting collaborative studies on vaccines for influenza, pertussis, rotavirus gastroenteritis, polio and pneumonia. So far, the group has achieved several works and contributed to the national vaccination program, including research on the immunogenicity of low doses of influenza vaccine among young children, the immunogenicity and effectiveness of the 2009 influenza pandemic vaccine among various risk groups, the interchangeability of live/inactivated polio vaccines, the health impact of influenza on pregnant women, and the monitoring of influenza vaccine effectiveness using case-control studies with a test-negative design. As part of the 18th Annual Meeting of the Japanese Society of Vaccinology, these accomplishments were featured in the Vaccine Epidemiology Symposium. This report summarizes the recent epidemiological studies on vaccine in Japan as a prologue to the next six papers collected from the symposium.



## 1. Introduction

After over 20 years of chaos with the influenza vaccination policy and debate over the effectiveness of the influenza vaccine in Japan, an influenza vaccination program targeting elderly people (≥65 years of age) was started in 2001 [1]. Currently, the vaccine coverage is estimated to remain constant at 50% or more in this age group. The total amount of influenza vaccine manufactured exceeded 33 kL (approximately 66 million doses) in 2013, as compared to 0.3 kL (approximately 0.6 million doses) in 1994 when the anti-vaccination campaign against the influenza vaccine was the most intense. During the influenza pandemic in 2009, 27 kL (approximately 54 million doses) of the pandemic vaccine was manufactured in addition to the already produced 23.13 kL (approximately 46.26 million doses) of the seasonal vaccine for that season. Thus, the importance of influenza vaccination against influenza infection appears to have become well understood, and the influenza vaccine production capacity has sufficiently recovered despite the anti-vaccination campaigns that still remain active to some extent. Over the course of these events, there is no doubt that the Vaccine Epidemiology Research Group created by the Ministry of Health, Labour and Welfare (MHLW) in 2002 has played an important role in demonstrating the solid scientific basis for influenza vaccination [1].

Recently, Japan has made major progress in conquering the vaccine gap by amending or promulgating the law and ordinances for general immunization programs. As such, five diseases have been newly listed as target diseases of the Preventive Vaccination Law since 2009. However, to achieve sound immunization programs, it is essential to promote mutual understanding between both the vaccine-providing and vaccine-receiving sides through the sharing of accurate information on vaccine efficacy and safety. Regrettably, however, poor-quality studies on vaccine effectiveness are still being reported, and their results are often being referred to without adequate scientific review.

*Abbreviations:* MHLW, Ministry of Health, Labour and Welfare of Japan; JSV, the Japanese Society of Vaccinology; ILI, influenza-like illness; HI, hemagglutination inhibition.

* Corresponding author at: College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan.
*E-mail address:* yos-hirota@healthcare-m.ac.jp (Y. Hirota).

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Based upon this history, the 18th Annual Meeting of the Japanese Society of Vaccinology (JSV) adopted the theme "To promote sound immunization programs: providing safe and effective vaccines and obtaining public understanding" and organized a symposium titled "Vaccine Epidemiology: Principles and Methods" [2]. Here, as a prologue to the next six papers collected from among the presentations in the symposium that focused on the methodology for vaccine effectiveness and related research, this report summarizes the current situation of vaccine effectiveness and safety studies in Japan from an epidemiological viewpoint.

## 2. Vaccine Epidemiology Research Group

### 2.1. Outline and framework

The Vaccine Epidemiology Research Group was established by the MHLW in 2002, immediately after the start of the influenza vaccination program targeting elderly persons in 2001, to assess the effectiveness of the influenza vaccine [1]. Following the success of its first research group, the group has remained active by modifying the study theme every 3 years (Table 1), expanding the objectives to several kinds of vaccines and involving more researchers from various fields. Presently, there is a total of 172 members, including epidemiologists, pediatricians, physicians, obstetricians, microbiologists, clinical pharmacologists and public health specialists, who are conducting collaborative studies on vaccines for influenza, pertussis [3,4], rotavirus gastroenteritis, polio and pneumonia [5].

### 2.2. Coordination

In addition to the routine studies performed by the individual members in their own research areas, there are research projects that are closely related to the national vaccination program, such as studies on the target groups of vaccinations, interchangeability among different vaccines for the same disease, and vaccination schedules. These studies generally require investigators with various specialties or from particular research institutes or organizations, and participants in large numbers or with certain characteristics, such as high-risk conditions.

Thus, the group has worked in close cooperation with institutes specialized in phase-1 trials from which experts in clinical pharmacology were invited. Their expertise as individual scientists and as a pillar of the institute is quite beneficial for the group, since vaccine research almost always requires the participation of otherwise healthy subjects. The group has also created a network of pediatric practitioners in the community who have a strong interest in vaccines and are therefore helpful in achieving studies by interacting with children and their parents for vaccinations, collecting blood samples, and conducting attack surveys, etc.

### 2.3. Development of two research methodologies

So far, two noteworthy methods of vaccine research have been developed by the group. One is the assessment of influenza vaccine efficacy based on "antibody efficacy" [6,7]. In this method, the frequency of influenza-like illness (ILI) or other clinical outcomes is compared between those who achieved a protective level of hemagglutination inhibition antibody (HI $\geq$ 1:40) and those who did not (HI < 1:40) after vaccination; this is in contrast to the typical comparison made between vaccinees and non-vaccinees. The product of the antibody efficacy and the achievement proportion which is the percentage of those who achieved a protective level of HI titer after vaccination among those with an HI < 1:40 before vaccination, is theoretically equivalent to the vaccine efficacy. Multivariate analysis for computing antibody efficacy, which includes variables representing HI titers against vaccine antigens together with potential confounders, makes it possible to estimate the clinical effectiveness of vaccine-induced antibodies by virus type or subtype without confirming strain-specific diseases. This method has two major strengths: first, vaccine efficacy can be calculated from the data of vaccinees alone, which is advantageous as the growing vaccine coverage among high-risk individuals makes it difficult to create an unvaccinated comparison group; second, the observation of clinical outcomes can be conducted in a double-blind manner, i.e., information on the HI titers is not known by the investigators or the study subjects, since antibody measurements are usually performed in the post-season.

The other method is the detailed analysis of antibody responses in immunogenicity studies. The generally used indices to illustrate immunogenicity, such as the geometric mean titer, sero-response proportion and the sero-protection proportion, are obtained through rather simple calculations as long as they are carried out for all of the subjects. However, studies for elucidating predictors of immunogenicity require substantially redundant and iterative calculations since the indices have to be computed separately for the different groups of individuals with or without specific characteristics, e.g., the age group, body mass index and severity among diabetes mellitus patients [8]. Such laborious work has discouraged researchers from exploring antibody responses in detail, and as a result, clinicians are obliged to provide and repeat explanations based on inferences and not on evidence when asked questions such as "Which was responsible for the lowered immune response: the underlying illness per se or the medicine for the treatment?" The group has made it possible to perform such iterative calculations more easily by developing a computational program that can be used to demonstrate whether some factors are actually associated with immunogenicity. Some outstanding studies have shown that prior seasonal influenza vaccination weakened the antibody responses to the 2009 pandemic vaccine [9], and that rituximab, a biological immune suppressant, rather than the disease per se, was the causal factor for lowered immunogenicity to the influenza vaccine in those with a hematological malignancy [10].

### 2.4. Accomplishments

The group has contributed to the national vaccination program by providing data obtained from epidemiological studies. Several examples are provided below.

**Table 1**
Chronology of the Vaccine Epidemiology Research Group organized by the Ministry of Health, Labour and Welfare, Japan.

| Fiscal year | Title of research | Grant amount (Japanese yen) |
|---|---|---|
| 2002–2004 | Appraisal of influenza vaccine effectiveness and vaccination policy in conformity with evidence-based medicine | 103,950,000 |
| 2005–2007 | Analytical epidemiologic study on the effectiveness of influenza and other vaccines and vaccination policy | 124,600,000 |
| 2008–2010 | Analytical epidemiologic study on influenza and other respiratory infections of concern in recent years | 216,837,000 |
| 2011–2013 | Analytical epidemiologic study on the effectiveness and safety of vaccines | 256,478,000 |
| 2014–2016 | Analytical epidemiologic study on vaccine effectiveness and safety and on vaccine-preventable disease control | 113,944,000 |

Compared to Western standards, the standard influenza vaccine dose for children in Japan had long been low (0.1 mL if <1 year old; 0.2 mL if 1–5 years old; 0.3 mL if 6–12 years old; and 0.5 mL if ≥13 years old). The group demonstrated the immunogenicity and safety of the vaccine doses according to Japanese and Western standards, and Japan subsequently switched to the same doses as those used in the Western standard in 2011 [11].

During the 2009 influenza pandemic, the group investigated the immunogenicity, effectiveness, and safety of the pandemic vaccine in study subjects with various characteristics, including young children and adolescents [12], the elderly and pregnant women [9], persons with motor and intellectual disability [13], those under hemodialysis, and patients with diabetes mellitus [8], chronic liver disease [14,15], hematological malignancies [10], or neuromuscular disorders [16]. The clinical effectiveness among pregnant women which was studied using the "antibody efficacy" method is worthy of note [17] as it would have been difficult to create an unvaccinated comparison group due to the prioritized use of vaccines for this group.

Besides the influenza vaccine, the group also played a decisive role in replacing the oral polio vaccine (OPV) with an inactivated polio vaccine (IPV). In Japan, OPV had been used until 2013 despite the strong calls to change to IPV because of the possibility of vaccine-associated paralytic polio (VAPP). The group investigated the interchangeability of OPV, DPT-IPV (Sabin) and IPV (Salk) by comparing the immunogenicities among four arms, i.e., one dose of OPV followed by three doses of DPT-IPV, one dose of OPV followed by three doses of IPV, two doses of DPT-IPV followed by two doses of IPV, and two doses of IPV followed by two doses of DPT-IPV. This study was successfully achieved after overcoming administrative and practical difficulties, i.e., the two test vaccines (DPT-IPV and IPV) were products from different manufacturers and neither had been licensed in Japan, and DPT-IPV had to be given in conformity with the vaccination schedule for DPT since many children had already received the dose(s) for the primary series of DPT in the general vaccination program.

Presently, the group is making great efforts in conducting two studies. The first study is the investigation of the health impact of influenza on pregnant women. In Japan, there has been no evidence on the extent of the effect of influenza on the health condition of pregnant women even though the World Health Organization recommended annual influenza vaccination for this group in its position paper in 2012 [18]. In fact, the proportion of hospitalized cases of pregnant women with influenza was quite low during the 2009 pandemic in Japan as compared to other countries [19]. A study adopting the "self-control method" has been completed with the cooperation of the Osaka Association of Obstetricians and Gynecologists involving more than 10,000 pregnant women; this represents a first since no large-scale database on pregnant women, such as the health maintenance organization, had been available in Japan. The final decision on whether routine influenza vaccination for pregnant women should be stipulated in the Preventive Vaccination Law will be made based on the findings of this study.

The second is the establishment of a monitoring system of influenza vaccine effectiveness; this is required as the level of detection of vaccine effectiveness varies depending on the time, place, and population. In a case-control study with a "test-negative (RT-PCR) control design", as are already being performed in the United States, Canada, Europe, Australia and New Zealand [20–24], vaccine effectiveness is being assessed among children aged <6 years who were recruited from five pediatric clinics in Osaka in the 2013–2014 season, and from 10 clinics in Osaka and Fukuoka in the 2014–2015 season. This study is expected to provide an abstract statement on influenza vaccine effectiveness and to enable comparisons with the data from other monitoring systems outside of Japan.

## 3. Frustrations of epidemiologists

When the fallacy that the influenza vaccine has no efficacy took over Japanese society, those who could theoretically explain why the influenza vaccine is so ineffective were regarded as influenza vaccine specialists. Their negative views were founded upon experimental findings, e.g., the nature of influenza virus to easily change its antigenic characteristics, the presence of antigenic differences between vaccines and circulating strains, and little or no antibody induction by inactivated vaccines on the surface of the respiratory tract mucosa. However, it is the principle that the efficacy and safety of any pharmaceutical products must be described based on data obtained solely from the human population. Thus, skepticism about vaccine efficacy resulting from the clinicians' low-quality studies that contained substantial disease misclassifications [25] was reinforced by the inference led from the experiments. In addition, the recent reports describing that seed viruses for the influenza vaccine are liable to mutations during incubation in eggs provided virologists with further speculative bases to negate influenza vaccine effectiveness. It is not easy for epidemiologists to overcome such negative inference generated from experimental findings. Epidemiological verification requires a large number of subjects and a long period of observation, while the results from those studies are generally regarded as the "gold standard" in evaluating medical intervention among human populations.

Although they are decreasing in number, low-quality studies containing substantial faults in the study design, conduct and analysis, that consequently suffer from serious validity problems, such as confounding and bias, are still being reported by clinicians. Furthermore, there are not many reviewers who can adequately judge those studies. In one clinic-based study that analyzed nearly 9000 vaccinees and non-vaccinees to investigate vaccine effectiveness against clinical influenza using a positive rapid diagnostic test, only the influenza attacks among the clinic visitors were taken into account, and those in non-visitors were not considered [26]. Thus, this study does not satisfy the principle that all study participants should be observed with equal intensity. A recent case-control study with a test-negative design using rapid diagnostic test results indicated no effectiveness for the influenza vaccine among infants aged 6–11 months [27]. However, this study suffered from selection bias due to a poor sampling scheme and a negative bias that originated from false-negative test results. It is regrettable that there are clinicians without even rudimentary knowledge of epidemiology who attempt to conduct case-control studies by themselves. Fortunately, however, a growing number of clinicians are trying to gain insight into the weaknesses of such attempts at epidemiological studies by consulting with epidemiologists.

Adverse events observed after vaccination, especially serious ones that are seen as a cluster, are also the concern of epidemiologists from the view of causality. In Japan, serious adverse events (SAEs) associated with vaccinations are usually explored by clinicians, as is the case for ordinal medicines, and presence or absence of causal relation is apt to be judged based on the interpretation of whether the connection between vaccination and SAEs can or cannot be explained by existing medical knowledge; unfortunately, vaccine-caused side effects are often unexplainable by current scientific information. An epidemiological approach seems to be crucial when examining whether an association is present or not, and if present, whether it is causal or not. Relatively new methods, such as case-crossover (CCO) studies and self-controlled case series (SCCS) studies, may bring about further clues to illuminate such

relationships [28,29]. However, the officials who are in charge of pharmaceutical affairs and clinicians who are in the position to remark on the SAEs often consider the judgment of causality to be their exclusive responsibility, and are unlikely to understand and apply epidemiological methods to their investigations.

## 4. Perspectives

When the symposium on influenza vaccine effectiveness was first held at the 9th Annual Meeting of the JSV in 2005 [1], a group of anti-vaccination activists took photographs point-by-point of slides projected in the conference hall to scrutinize potential faults in the presentation. Afterwards, they sent open letters addressed to the organizer of the symposium and the chairperson of the meeting to accuse them of the "faults" that they believed to have found. In contrast, at the symposium in 2014, we were able to enjoy fruitful discussions in an academic atmosphere. The public understanding of and attitude toward vaccines and vaccination has actually changed, but difficulty in establishing adequate scientific evidence that is firm enough to convince the general public remains a major obstacle in promoting the vaccination program in Japan.

The difficulties we have so far experienced with respect to the influenza vaccine and vaccination are considered to represent the general challenges faced with any vaccine. The maintenance and expansion of the present framework of the Vaccine Epidemiology Research Group will contribute to the creation of solid vaccination programs at the national level. The following six articles related to the subjects of the symposium will undoubtedly convey to the readers not only information on the present research activities of the group, but also insight into the obstacles related to the national vaccination program in Japan.

## Conflict of interest

The author declare that there is no conflict of interest.

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## References

[1] Hirota Y, Kaji M. History of influenza vaccination programs in Japan. Vaccine 2008;26:6451–4.
[2] Hirota Y. Announcement for and invitation to the 18th annual meeting of Japanese Society of Vaccinology (JSV). Vaccine 2014;32:5888.
[3] Hara M, Okada K, Yamaguchi Y, Uno S, Otsuka Y, Shimanoe C, et al. Immunogenicity and safety after booster vaccination of diphtheria, tetanus, and acellular pertussis in young adults: an open randomized controlled trial in Japan. Clin Vaccine Immunol 2013;20:1799–804.
[4] Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y. Effectiveness of acellular pertussis vaccine in a routine immunization program: a multicenter, case-control study in Japan. Vaccine 2015;33:1027–32.
[5] Kondo K, Suzuki K, Washio M, Ohfuji S, Fukushima W, Maeda A, et al. Association between monovalent influenza A (H1N1) pdm09 vaccine and pneumonia among the elderly in the 2009-2010 season in Japan: a case-control study. Hum Vaccin Immunother 2015;11:1088–93.
[6] Hirota Y, Kaji M, Ide S, Kajiwara J, Kataoka K, Goto S, Oka T. Antibody efficacy as a keen index to evaluate influenza vaccine effectiveness. Vaccine 1997;15:962–7.
[7] Hara M, Tanaka K, Kase T, Maeda A, Hirota Y. Evaluation of seasonal influenza vaccination effectiveness based on antibody efficacy among the institutionalized elderly in Japan. Vaccine 2010;35:5664–8.
[8] Egawa Y, Ohfuji S, Fukushima W, Yamazaki Y, Morioka T, Emoto M, et al. Immunogenicity of influenza A(H1N1)pdm09 vaccine in patients with diabetes mellitus: with special reference to age, body mass index and HbA1c. Hum Vaccin Immunother 2014;10:1187–94.
[9] Ohfuji S, Fukushima W, Deguchi M, Kawabata K, Yoshida H, Hatayama H, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine among pregnant women: lowered antibody response by prior seasonal vaccination. J Infect Dis 2011;203:1301–8.
[10] Ide Y, Imamura Y, Ohfuji S, Fukushima W, Ide S, Tsutsumi C, Koga M, Maeda K, Hirota Y. Immunogenicity of a monovalent influenza A(H1N1)pdm09 vaccine in patients with hematological malignancies. Hum Vaccines Immunother 2014;10:1–8.
[11] Mugitani A, Ito K, Irie S, Eto T, Ishibashi M, Ohfuji S, et al. Immunogenicity of the trivalent inactivated influenza vaccine in young children less than 4 years of age, with a focus on age and baseline antibodies. Clin Vaccine Immunol 2014;21:1253–60.
[12] Kobayashi M, Ohfuji S, Fukushima W, Maeda A, Maeda K, Fujioka M, et al. Immunogenicity and reactogenicity of a monovalent inactivated 2009 influenza A vaccine in adolescents: with special reference to pre-existing antibody. J Pediatr 2012;160:632–7.
[13] Hara M, Hanaoka T, Mizushima T, Honma J, Maeda K, Ohfuji S, et al. Diminished immunogenicity to pandemic H1N1 2009 influenza vaccine in subjects with severe motor and intellectual disability. Vaccine 2011;29:8323–9.
[14] Ohfuji S, Fukushima W, Tamori A, Maeda K, Maeda A, Hirota Y. Immunogenicity of influenza A(H1N1)pdm09 vaccine and the associated factors on lowered immune response in patients with hepatitis C. Influenza Other Respi Viruses 2013;7:456–65.
[15] Ohfuji S, Fukushima W, Sasaki Y, Tamori A, Kurai O, Kioka K, et al. Influenza A (H1N1)pdm09 vaccine effectiveness and other characteristics associated with hospitalization in chronic liver disease patients. Liver Int 2014;34:700–6.
[16] Saito T, Ohfuji S, Matsumura T, Saito T, Maeda K, Maeda A, et al. Safety of a pandemic influenza vaccine and immune response in patients with Duchenne muscular dystrophy. Intern Med 2015;54:1199–205.
[17] Fukushima W, Ohfuji S, Deguchi M, Kawabata K, Hatayama H, Yoshida H, et al. Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: a prospective observational study assessing antibody efficacy. Vaccine 2012;30:7630–6.
[18] WHO. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Record 2012;87:461–76.
[19] WHO. Transmission dynamics and impact of pandemic influenza A(H1N1) 2009 virus. Wkly Epidemiol Record 2009;84:481–4.
[20] Treanor JJ, Talbot HK, Ohmit SE, Coleman LA, Thompson MG, Cheng PY, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis 2012;55:951–9.
[21] Skowronski DM, Janjua NZ, De Serres G, Dickinson JA, Winter AL, Mahmud SM, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. Euro Surveill 2013;18 (5).
[22] Kissling E, Valenciano M, Falcao J, Larrauri A, Widgren K, Pitigoi D, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Euro Surveill 2009;14(44).
[23] Carville KS, Grant KA, Sullivan SG, Fielding JE, Lane CR, Franklin L, et al. Understanding influenza vaccine protection in the community: an assessment of the 2013 influenza season in Victoria, Australia. Vaccine 2015;33:341–5.
[24] Turner N, Pierse N, Huang QS, Radke S, Bissielo A, Thompson MG, et al. Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014. Euro Surveill 2014;19(42).
[25] Hirota Y, Kaji M. Scepticism about influenza vaccine efficacy in Japan. Lancet 1994;344:408–9.
[26] Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Tsuchimoto T, et al. A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001–2002 influenza season. Vaccine 2003;21:4507–13.
[27] Shinjoh M, Sugaya N, Yamaguchi Y, Tomidokoro Y, Sekiguchi S, Mitamura K, et al., Keio Pediatric Influenza Research Group. Effectiveness of trivalent inactivated influenza vaccine in children estimated by a test-negative case-control design study based on influenza rapid diagnostic test results. PLoS ONE 10(8): e0136539. doi: 10.1371/journal.pone.0136539.
[28] Ki M, Park T, Yi SG, Oh JK, Choi BY. Risk analysis of aseptic meningitis after measles-mumps-rubella vaccination in Korean children by using a case-crossover design. Am J Epidemiol 2003;157:158–65.
[29] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. VSD rapid cycle analysis influenza working group. signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. Vaccine 2012;30:2024–31.