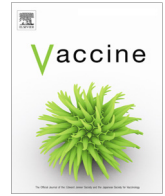




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## Review

# Implementing vaccination policies based upon scientific evidence in Japan

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## ABSTRACT

The theme of the 24th Annual Meeting of the Japanese Society for Vaccinology was “Sustainable Future Medical Care Created by Vaccines.” This theme includes topics such as the proposal to reduce the medical costs incurred by societies with aging populations through prophylactic vaccination. The coronavirus disease 2019 (COVID-19) pandemic alerted us to the important roles that preventive measures, such as vaccines, play in fighting infectious diseases. In order to inform the public of the benefits of vaccines, it is important to provide society with information regarding new vaccine developments, adjuvants, the cost–benefit ratio of vaccine introduction, and vaccine effectiveness and safety. Clinical research is essential for obtaining evidence of vaccine effectiveness and safety. The United States Centers for Disease Control and Prevention (CDC) conducts active surveillance in defined areas before and after the introduction of vaccines and documents the reduction in infection rates as a measure of vaccine effectiveness. However, vaccine efficacy and side effects may vary by country and ethnicity. Therefore, it is necessary for individual countries to develop their own evidence-based surveillance programs. We have studied vaccine efficacy and documented side-effects observed in patients for the varicella and rotavirus vaccines in Japan. This review outlines the importance of providing scientific evidence for vaccine effectiveness and safety.

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## 1. Introduction

In most developed countries, including Japan, the combination of a low birthrate and an aging population is a major societal problem that has caused a significant increase in medical expenses for aging population. Therefore, the Japanese government has outlined three visions and plans of action for health care that are to be achieved by 2035. One vision states that prophylactic treatment

based on vaccination is important for creating a sustainable society. The COVID-19 outbreak, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in Wuhan, China, in December of 2019 [1,2]. The outbreak spread rapidly around the world, and the WHO has declared it a pandemic. Because no reliable COVID-19 treatment has yet been established, vaccination has become the focus of public attention. New vaccine platforms, such as messenger RNA and viral-vector vaccines, are being used for currently licensed vaccines [3,4]. In general, it takes 10–30 years to produce a licensed vaccine after starting basic preclinical studies. However, the introduction of new vaccine development

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technologies such as the mRNA vaccine strategy and the Operation Warp Speed initiative enabled successful development of several licensed COVID-19 vaccines in a much shorter period of time [5]. These vaccines will likely be introduced in Japan after obtaining licensure in the United States and European countries. However, because variables pertaining to the COVID-19 outbreaks in our country are different from those countries, it is important to evaluate vaccine efficacy and safety based upon our own scientific evidence. Therefore, it is imperative to generate evidence regarding vaccine efficacy and safety based on data from the Japanese population.

## 2. Effectiveness of the varicella vaccine

The live-attenuated Oka varicella vaccine was developed by Japanese researchers in 1974 [6]. This vaccine has been administered in Japan to healthy children on a voluntary basis for many years and was licensed for use in the United States by the Food and Drug Administration in 1995. At that time, the United States Advisory Committee on Immunization Practice (ACIP), a committee which gives recommendation to the CDC, recommended that all healthy, susceptible children receive one dose of universal varicella vaccination at 12–18 months of age. Prior to implementation of universal varicella vaccination, the CDC performed active surveillance of varicella in three cities across the United States to collect scientific data for evaluation of the efficacy and safety of the vaccine [7]. The typical seasonal epidemic pattern and peak number of cases gradually decreased each year after implementation of universal vaccination. In 1999, the number and rate of varicella cases and hospitalizations were markedly lower relative to prior years. From 1995 to 2000, varicella cases declined 71%, 84%, and 79% in Antelope Valley, Travis County, and West Philadelphia, respectively. In addition, the number of severe complications [8] and fatal cases decreased, and medical costs related to varicella were reduced [9].

In spite of the remarkable decrease in varicella cases observed after implementing universal vaccination, the reduction in opportunities for natural boosters due to community exposure resulted in waning immunity in vaccine recipients following one dose of varicella vaccine. The annual rate of breakthrough varicella cases significantly increased with time post-vaccination, from 1.6 cases per 1000 person-years (95% CI, 1.2–2.0) at 1 year post-vaccination to 9.0 per 1000 person-years (95% CI, 6.9–11.7) and 58.2 per 1000 person-years (95% CI, 36.0–94.0) at 5 and 9 years post-vaccination, respectively [10]. This alarming trend suggested that: (1) administering only one dose of the vaccine may induce waning immunity, causing an increase in breakthrough varicella cases; and (2) an additional dose of vaccine is necessary to boost immunity. In 2007 ACIP recommended that all children receive a second dose of varicella vaccine [11], because this second immunization would provide additional protection from both primary vaccine failure and waning vaccine-induced infection. These outcomes clearly indicate that evidence-based scientific data and continued monitoring of vaccine effectiveness are extremely important metrics to consider when implementing universal vaccine policies.

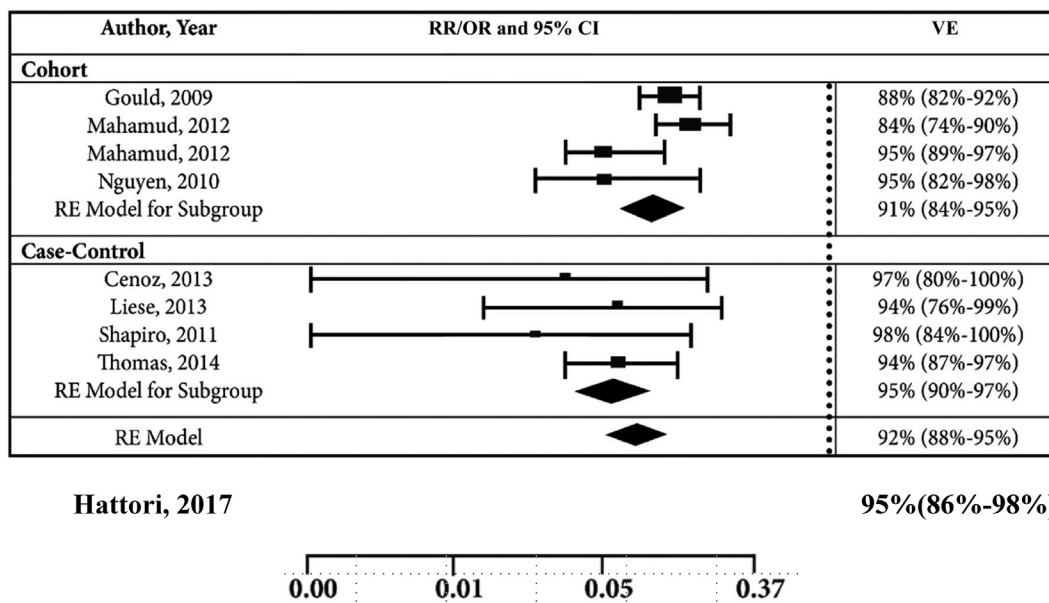
A meta-analysis of vaccine effectiveness (VE) that primarily used data from the United States and Europe recommended universal immunization with the Varivax or Varilrix vaccinations [12]. By contrast, Japan uses only the original Oka/Biken vaccine. Though long-term persistence of varicella zoster virus-specific immunity is observed [13,14], a recent increase in the number of breakthrough varicella cases has raised concerns about vaccine efficacy in Japan [15]. Because varicella vaccine effectiveness may be country-specific, we conducted a matched case-control study to determine the VE of the Oka/Biken varicella vaccine in Japan

immediately after implementation of the universal immunization program [16]. Patients were under 15 years of age, and the control group included patients who visited the same practice, for different reasons, within 2 weeks of the confirmed varicella-positive patients. Swab samples were collected from patients suspected of varicella, and molecular diagnostic assays were used to confirm varicella infection. After adjusting for potential confounding variables, the adjusted VE for one and two inoculations were 76.9% (95% CI: 58.1–87.3%;  $P < 0.001$ ) and 94.7% (95% CI: 86.0–98.0%;  $P < 0.001$ ), respectively. Although administration of one dose was insufficient to completely prevent varicella infection, two doses significantly improved VE, as observed previously in Western countries (Fig. 1) [12]. Further monitoring of varicella-positive patients has shown that the levels of breakthrough varicella continue to rise in Japan [17]. To control varicella completely in Japan, it is necessary to immunize older children who are unvaccinated or who only received one dose. In addition, because breakthrough varicella cases present with very mild clinical symptoms, precise diagnosis is difficult. Hence, reliable point-of-care tests, such as the loop-mediated isothermal amplification method [18], are needed to accurately monitor varicella outbreaks.

## 3. Effectiveness of the rotavirus vaccine

Rotavirus (RV), a leading cause of gastroenteritis (GE) in children, causes substantial morbidity and mortality worldwide. In addition to the disease burdens related to hospitalization and outpatient visits caused by RVGE-induced dehydration, severe complications such as encephalitis [19] and sudden unexpected death [20] are also of concern in developed countries including Japan. To decrease this disease burden, two live-attenuated RV vaccines were introduced. Rotarix (RV1; GlaxoSmithKline) is an orally administered monovalent live-attenuated vaccine derived from human RV, and RotaTeq (RV5; MSD) is an orally administered live vaccine with a backbone derived from bovine RV. Although the vaccines are expected to cross-protect against other RV genotypes, several large-scale molecular epidemiological studies have identified genotypic changes in RV after introduction of the vaccine in several countries [21–23], suggesting possibility of viral escape due to vaccine-induced immune pressure. These observations emphasize the importance of long-term follow-up of vaccine efficacy and RV genotype changes in order to effectively control RV infection. Furthermore, because different vaccines have been introduced in each region, molecular epidemiology and vaccine efficacy should be analyzed locally.

RV vaccination has been available in Japan since November of 2011. Initially, the RV vaccine was administered on a voluntary basis, and several local governments supplemented the cost of vaccination to increase vaccine coverage. Consequently, vaccine rates have gradually increased, and the number of RVGE patients has declined. Vaccination support by the city of Nagoya resulted in a remarkable decrease in the number of RVGE-related hospitalizations and outpatient visits in the city [24]. Universal RV immunization was implemented in October of 2020 after reviewing the results from several studies that demonstrated the impact of vaccination in Japan [25,26]. Data demonstrating vaccine safety, in particular the observation that the benefits of RV vaccination overwhelm the risk of RV vaccine such as vaccine-related intussusception [27–28], were essential to promoting universal vaccination. The baseline incidence of intussusception is higher in Japan than in Western countries. The number of intussusception cases did not significantly increase after introduction of the RV vaccine in Japan, which is consistent with systematic literature review of the studies that investigated the association between the RV vaccine and intussusception [29].



**Fig. 1.** Two-dose varicella vaccine effectiveness for prevention of all varicella, by study design, including Japanese data. This figure is modified from the original meta-analysis data [12].

Scientific evidence demonstrating that vaccination reduces RVGE should continue to emerge now that universal RV vaccination has been implemented. Because parents and physicians in Japan can choose between two different vaccines, RVGE patients fall into three different groups: patients who received RV1, those who received RV5, and unvaccinated patients. This situation is different from most countries that have introduced a national RV immunization program. An RVGE outbreak occurred during the 2018/2019 season in Aichi Prefecture in Japan, and we compared the molecular epidemiology of RV and clinical features manifested between the three different groups of RVGE patients (submitted manuscript). Among the 110 patients, there were 27, 28, and 55 in the RV1-vaccinated, RV5-vaccinated, and unvaccinated groups, respectively. The most frequent genotype was G8P (92/110 patients, 83.6%) [8]. Genotype distributions did not significantly differ among the groups ( $P = 0.125$ ). The mean Vesikari score was significantly lower for RV1-vaccinated (7.1) and RV5-vaccinated patients (6.4) than for unvaccinated patients (10.2) ( $P < 0.001$ ). Vaccination status was not significantly correlated with RV genotype distribution. RV vaccination prior to infection reduced infection severity in this cohort, based on the Vesikari score analysis. Because RV vaccines can decrease disease severity but cannot completely prevent viral infection, eradication of RV infection is currently impossible. Therefore, continued monitoring of vaccine efficacy, viral epidemiology, and clinical findings is needed to control RVGE by RV vaccination.

**4. Conclusion**

Japan is predicted to have an aging population for the foreseeable future. Concurrent with this societal shift, medical expenses will continue to increase and become a serious social problem. Therefore, the role that vaccines will play in disease prophylaxis is expected to expand. In order for vaccines to be widely accepted by the public, it is important to continue to establish and disseminate domestic evidence of vaccine efficacy and safety.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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