

COMMENTARY



Resumption of active recommendation of the human papillomavirus vaccine in Japan and future challenges for the National Immunization Program

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ABSTRACT

Japan's immunization program resumed proactively recommending the use of the human papillomavirus (HPV) vaccine nationwide in April 2022, after suspending this recommendation in June 2013. The promotion of catch-up vaccinations is an urgent issue to reduce the increase in cervical cancer and other cancers caused by low vaccination rates. In addition, the National Immunization Program still has issues to be considered, such as the adoption of the 9-valent vaccine, establishment of an appropriate number of vaccinations according to age, and routine immunization of males. There is a history of eliminating the use of the measles, mumps, and rubella vaccine and the mouse brain-derived, purified inactivated Japanese encephalitis vaccine, as well as suspending the HPV vaccine recommendation in Japan. These decisions have led to the current preventable infectious disease burden. In order to make the right policy decisions based on science-based assessments, it is necessary to establish a safety assessment platform to evaluate the causal relationship between vaccines and adverse events following immunization. Information technology, which has been promoted with the coronavirus disease 2019 vaccine in the current pandemic, may assist in providing more detailed vaccine safety evaluations for other vaccines.

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Introduction

Japan's immunization program, resumed proactively recommending the use of the human papillomavirus (HPV) vaccine nationwide in April 2022, after suspending this recommendation in June 2013.¹ As a part of the program, municipalities send vaccination vouchers to individuals who are eligible for vaccine administration. In spite of the ongoing suspension, the vaccination rate, which fell to 0.3% among females in the target age group of 11–16 years in 2016, has gradually improved in recent years. In 2020, 83,735 females received the first dose of HPV vaccine in the national immunization program. Therefore, the estimated immunization coverage has improved to approximately 15.9%.² This may be due to governmental efforts to convey information about the benefits of HPV vaccination to the eligible population and their caregivers, as well as local educational programs.³ Females aged 16–24 years, who had missed their opportunity to receive the free HPV vaccination under the national immunization program when they were 11–16 years old, due to the recommendation suspension, will now have the opportunity to receive the missed vaccinations over the last three years, free of cost. Furthermore, females who have received these vaccines at their own expenses, may apply for reimbursement.

Remaining HPV vaccination program challenges

Japan's HPV vaccine program has limitations and areas to be improved. For example, in many countries, two doses are administered to people under 14 years of age, which has

been shown to induce an adequate immune response; in contrast, Japan requires three doses for all eligible individuals.⁴ Furthermore, the WHO's Strategic Advisory Group of Experts on Immunization reviewed the immunogenicity and recommended two doses of HPV vaccine for all ages, except the immunocompromised, and one or two doses for those under age 20.⁵ Decreasing the number of doses can reduce adverse events following immunization and costs. Additionally, only bivalent and quadrivalent HPV vaccines are available as part of the immunization program, and the 9-valent HPV vaccine, which became available in February 2021, is not used. Although use of the 9-valent vaccine is being considered by the Council, a stable supply of these vaccine products is unavailable because of increasing global demand. Of note, because the more effective 9-valent vaccine is not used in the program, eligible individuals should be encouraged to receive the quadrivalent vaccine at the appropriate time. Finally, because the immunization program targets only females, it is necessary to consider offering immunization to males to ensure equity among sexes and to prevent cancers other than cervical cancer. The 9-valent HPV vaccine is approved for the prevention of HPV-related cervical, vaginal, vulvar, anal, oropharyngeal, and other head and neck cancers in the United States.⁶ And oropharyngeal cancer (OPC) is now the most common HPV-associated cancer. During 1999–2015 cervical cancer incidence rates decreased 1.6% per year, and OPC incidence rates increased 2.7% per year among males and 0.8% per year among females in the United States.⁷

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The age-adjusted incidence rate of cervical cancer per 100,000 population in Japan was 14.1 in 2017 and is increasing.⁸ In addition, the declining vaccination rate among Japanese women who were affected by the withholding of active recommendations is predicted to increase to approximately 25,000 cervical cancer cases and more than 5,000 deaths in the future.⁹ Thus, utilizing the catch-up programs by early promotion of vaccination to women under the age of 24 who have not yet been vaccinated, is required.

Active recommendation was suspended for approximately nine years; partially because of the mandatory reporting of adverse events following immunization, which was enacted after amendments were made to the Immunization Law that came into effect in April 2013. Under this system, reports could be made by not only physicians who can perform medical evaluation, but also by third parties such as vaccinated individuals, their guardians and others, without proper medical evaluation of the duration of time since vaccination.³ Adverse event reports, including those from past vaccinations, rapidly increased within a short period, making it necessary to temporarily suspend the active vaccination recommendation, according to the precautionary principle. However, research findings indicate that this suspension has been excessively long and may have harmed many females.^{4,9} Recent statistics have shown that invasive cervical cancer is decreasing in many countries. However, an increasing incidence of cervical cancer has been reported in Japan, especially among women in their reproductive years.¹⁰ It is also estimated that the reduction in vaccination coverage from 2013 to 2019 would result in 24,600–27 300 additional cervical cancer cases and 5 000–5 700 deaths compared to if coverage had remained at about 70% after 2013.⁹ One possible reason for the failure to make a rapid decision is the influence of media coverage, which led to the spread of false risk perceptions among the general public, resulting in lawsuits and political disputes.¹¹

Past cases of withholding active recommendations

Similar cases of withholding active recommendations have occurred in the past, including the measles, mumps, and rubella vaccine, which was discontinued in April 1993, after its introduction in April 1989, because of the high frequency of aseptic meningitis caused by the mumps virus following immunization. Therefore, the mumps vaccine is no longer included in the national immunization program.¹² As a result, many cases of epidemic parotitis are reported each year from approximately 3,000 pediatric sentinel medical facilities. From 2015, when 81,046 cases were reported, to 2016, when 158,996 cases were reported, at least 359 individuals were newly diagnosed with hearing loss due to mumps, based on a survey of medical facilities with otolaryngology departments across Japan.^{13,14} Additionally, reports of acute disseminated encephalomyelitis following Japanese encephalitis vaccination (6 cases in 2003 and 2 cases in 2004) led to the suspension of active recommendations from May 2005 to April 2010, with the vaccination rate decreasing to below 4% in 2006.¹⁵

Improving the evaluation system for the national immunization program

To date, Japan's immunization program policy decisions have been made without adequate scientific evaluation of the causal relationship between vaccines and reported adverse events following immunization.

In addition to the adverse event reporting system introduced in 2013, a system to quantitatively assess the risk of reported adverse events, by collecting information on non-vaccinated individuals matched with the social background of the vaccinees, needs to be established. It is essential to develop a safety evaluation infrastructure such as "Post-Licensure Rapid Immunization Safety Monitoring," which can rapidly detect signs of epidemiological changes after vaccine introduction, even for rare diseases, using the medical insurance system. Most immunization services, other than the national program in Japan, are conducted as private medical services, and it is difficult to obtain information linked to the medical insurance system. On the other hand, in recent years, technology has progressed under the novel coronavirus disease 2019 (COVID-19) pandemic. It has become possible for the government to monitor immunization status in real-time by integrating immunization information registered by each municipality, using the unique national number assigned to each resident. This information is also used to issue official digital vaccination certificates using smartphones. The management and utilization of immunization records using these IT technologies should not be limited to the COVID-19 vaccine, but should be extended to vaccines in general.

Conclusion

Although active recommendation of the HPV vaccines in Japan has resumed after approximately nine years, decisions regarding vaccine policies may greatly impact public health by reducing immunization rates. Therefore, to avoid repetition of past problems, it is essential to expand the adaptation of innovative information technology. Such technology has increasingly being used for COVID-19 measures, can raise awareness regarding the importance of immunization, and formulate future immunization policies according to the risk-benefit balance of society as a whole based on objective and quantitative research findings.

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