Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Sayaka Ikeda, Yutaka Ueda, Asami Yagi, Shinya Matsuzaki, Eiji Kobayashi, Tadashi Kimura, Etsuko Miyagi, Masayuki Sekine, Takayuki Enomoto & Kazuya Kudoh (2019) HPV vaccination in Japan: what is happening in Japan?, Expert Review of Vaccines, 18:4, 323-325, DOI: 10.1080/14760584.2019.1584040

To link to this article: https://doi.org/10.1080/14760584.2019.1584040

Accepted author version posted online: 15 Feb 2019.
Published online: 22 Feb 2019.

EXPERT REVIEW OF VACCINES
2019, VOL. 18, NO. 4, 323–325
https://doi.org/10.1080/14760584.2019.1584040

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EDITORIAL

HPV vaccination in Japan: what is happening in Japan?

Sayaka Ikeda[a], Yutaka Ueda[b], Asami Yagi[b], Shinya Matsuzaki[b], Eiji Kobayashi[b], Tadashi Kimura[b], Etsuko Miyagi [c], Masayuki Sekine[d], Takayuki Enomoto[d] and Kazuya Kudoh[a]

[a]Department of Gynecology, Tama-Hokubu Medical Center, Tokyo Metropolitan Health and Medical Treatment Corporation, Higashimurayama, Tokyo, Japan; [b]Department of Obstetrics and Gynecology, Osaka University, Osaka, Japan; [c]Department of Obstetrics and Gynecology, Yokohama City University, Yokohama, Japan; [d]Department of Obstetrics and Gynecology, University of Niigata, Niigata, Japan

ARTICLE HISTORY Received 6 November 2018; Accepted 13 February 2019

KEYWORDS HPV vaccine; cervical cancer; governmental suspension of recommendation; effectiveness; adverse events

1. Cervical cancer in Japan

In Japan, the morbidity and mortality of cervical cancer have recently been on the rise. According to the Japanese Center for Cancer Control and Information Services, approximately 10,490 people were diagnosed with cervical cancer in 2014 [1], and 2,710 people died from it in 2016 [2]. The incidence rate of cervical cancer by age has increased most acutely in younger women [3]. Looking at the age-adjusted mortality rate over the past 10 years, death from cervical cancer has increased by 9.6%. Thus, in Japan, we are facing a problem of rising cervical cancer death rate, while the mortality rates in the five other major cancers have declined [4].

In Japan, a biennial cytology screening for cervical cancer is recommended for all women over age 20. Although the recent rise in cervical cancer is occurring predominantly in women in their 20s, the rate of having a cervical cancer screening is only 22.2% in that age group, which is low when compared with other developed nations [5].

Cervical cancer is mainly caused by persistent infection with human papilloma virus (HPV). There are more than 100 types of HPV, of which 13 are called high-risk types. They are the most strongly linked to the onset of cervical cancer. HPV has retrospectively been detected in almost 100% of cervical cancers in Japan, especially HPV 16 and 18, which together account for around 65% of all cervical cancer cases in Japan[6]. Furthermore, HPV 16 and 18 are detected in 90% of patients with cervical cancer in their 20s and in 76% in their 30s [6]. HPV-DNA tests are still in the clinical research trails, and they have not yet been in widespread use in Japan.

In recent years, vaccines for cervical cancer that can prevent HPV 16 and 18 infection have been developed. Their cancer preventive efficacies have been well demonstrated in various countries around the world. The cervical cancer vaccines that have been most applicable in Japan are the bi-valent Cervarix (for HPV strains 16, 18) and the quadra-valent Gardasil (6, 11, 16, 18). The newest nine-valent HPV vaccine has not yet been approved in Japan.

2. The state of affairs of HPV vaccination in Japan

In Japan, the percentage of women getting a cervical cancer screening is low, while the incidence of cervical cancer is increasing. Therefore, the nationwide introduction of HPV vaccination was expected to bring cervical cancer under control. Subsidies from local and national governments for an HPV vaccination program commenced in 2010, and the HPV vaccine was introduced for routine use in the national immunization program for girls aged 12–16 years in April of 2013. However, repeated news reports about the occurrence of diverse symptoms, including chronic pain, motor impairment and other symptoms in some vaccine recipients arose shortly thereafter. As a result, on 14 June 2013, just two months later after the vaccine recommendation had begun, the Ministry of Health, Labour and Welfare (MHLW) announced, a 'Suspension of the proactive recommendation for routine use of the HPV vaccine in the national immunization program' [7]. When the suspension was first announced, MHLW said it would continue until proper information could be provided to the public. However, the suspension has been continuing until today for more than five years. Due to these events, the HPV vaccination rate among younger women has dropped sharply from its peak of about 70% in 2013 to a current rate of 1% or less for those born in after 2002 [8].

Following the sensational media reports in March of 2013, concerning the HPV vaccine's putative adverse events, newspaper articles about HPV vaccination became more negative, and positive articles became less frequent [9]. These events combined to negatively affect Japanese mothers' intention to vaccinate their adolescence daughters. It was revealed that, among Japanese mothers, their intention to inoculate their daughters has been steadily declining over time since 2013, triggered by the suspension, and this negative intent would likely to persist, whether the governmental recommendation would ever be reinstated or not [10]. This reaction has not only been seen in Japan, but also in Denmark, where there was a similar decline in HPV vaccination. The case in Denmark was followed by allegations of suspected adverse reactions. The point of the rapid decline in vaccination uptake in Denmark coincided with an increase in both an increase in online Google searches for 'HPV side effects' and media coverage with negative content. It has been suggested that the possibility of influence of media coverage on vaccination intention [11].

CONTACT Yutaka Ueda ZVF03563@nifty.ne.jp Department of Obstetrics and Gynecology, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

In this circumstance in Japan, the World Health Organization (WHO)'s Global Advisory Committee on Vaccine Safety (GACVS) commented that young women were being left vulnerable to preventable HPV-related cancers, and that the policy decisions based on the weak evidence were leading to lack of use the safe and effective vaccines, potentially resulting in real harm [12]. A strategy to prevent cervical cancer through effective screening is essential, and all efforts to increase examination rates should be continued. However, finding new ways to improve screening rates among young women has been seen as a critical national health problem in Japan. Notably, for a generation of young women, a free-coupon program for cervical cancer screening was effective in increasing the first-time screening participation rate. However, it didn't quite meet the expectations in consecutive screenings [13]. As the incidence of cervical cancer in Japan has increased more in younger women, the HPV vaccine was expected to prevent the HPV infection. It should be noted that HPV vaccine litigation has currently being conducted in four Japanese cities: Tokyo, Nagoya, Osaka, and Kyushu [14].

3. Safety and efficacy of HPV vaccination

To better understand the significance and health impact of the purported adverse symptoms from the HPV vaccine, a national epidemiological study of the general population in Japan was conducted by a research arm of the MHLW. In the research, similar numbers of girls with the same symptoms were reported in both vaccinated and unvaccinated girls. 20.4 cases were reported per 100,000 women aged 12–18 as they presented with the symptoms which they claimed to be associated with the HPV vaccine. The rate of these diverse adverse symptoms occurring in the general population of girls of this age-group increased to 46.2 cases when the cases with unknown HPV vaccination history were included [15]. Also there is a research conducted in Nagoya, of the potential association between the HPV vaccine and the reported symptoms. It showed no significant increase in occurrence of any of 24 reported putative post-HPV-vaccination symptoms. The vaccine was associated with increased age-adjusted odds of hospital visits for 'abnormal amount of menstrual bleeding' (OR: 1.43, 95% CI: 1.13–1.82), 'irregular menstruation' (OR: 1.29, 95% CI: 1.12–1.49), 'severe headaches' (OR: 1.19, 95% CI: 1.02–1.39), and chronic, persisting 'abnormal amount of menstrual bleeding' (OR 1.41, 95% CI: 1.11–1.79). None of these symptoms significantly influenced school attendance and no accumulation of these symptoms was observed. As a result, it suggested no causal association between the HPV vaccine and any of the 24 previously reported adverse symptoms [16].

In regard to the vaccine's efficacy, it has been demonstrated that HPV vaccination leads to a significant reduction in the incidence of abnormal cervical cytological findings, compared to those who were unvaccinated. And more importantly, a significant reduction has been seen in the histological diagnosis of CIN2 or worse [17,18]. A dynamic decrease has been demonstrated in the year-over-year rate of abnormal screening results in association with the introduction of the HPV vaccine, *i.e.*, for the birth-year-dependent change in cervical cancer risk[19]. The targets during 2014–2019 were, or will be, those born in 1994–1999, *i.e.*, those who came of age during a period with the highest HPV immunization rate. The rate of abnormal findings in cervical cytology increased slightly from 3.68% in 2010 (birth year: 1990) to 4.35% in 2013 (birth year: 1993). However, it dramatically dropped to 2.99% in 2014 (birth year: 1994) and 3.03% in 2015 (birth year: 1995). On average, the rate in 2010–2013 was 3.96%, but it dropped significantly down to 3.01% in 2014–2015 ($p = 0.014$) [19]. On a worldwide scale, approximate maximal reductions of 90% for HPV 6/11/16/18 infection, 45% for low-grade cytological cervical abnormalities, and 85% for high-grade histologically-proven cervical abnormalities have been reported [20]. The GACVS has systematically investigated the safety concerns with HPV vaccines, and stated that it has not found any safety issues that would alter their recommendations for use of the vaccine [12].

Based on scientific evidence, the Japanese Society of Obstetrics and Gynecology have stated several times that it is necessary to have both the HPV vaccine and regular cervical cytology screenings to prevent cervical cancer. They have also strongly demanded a reinstatement of Japan's governmental recommendation of HPV vaccination [21]. Seventeen Japanese academic societies including the Japanese Pediatric Society have also sought a strong endorsement for HPV vaccination [22]. We should note that the strong negative publicity surrounding the HPV vaccine even affected the attitudes of Japan's obstetricians and gynecologists at first. However, their opinions about the HPV vaccine have been gradually improved [23], potentially leading to a more positive future re-engagement for HPV vaccination.

As a support system for those who might have any symptom after HPV vaccination, medical consultation rooms have now been set up at 73 facilities, covering all the prefectures in Japan. The Japanese Medical Association and the Japanese Association of Medical Science have published medical guidance regarding the symptoms that might occur after HPV vaccination [24].

4. Conclusions

Both the effectiveness and the safety of HPV vaccine have been scientifically demonstrated worldwide. However, Japan's health regulatory body, the MHLW, has not yet been willing to reverse their 2013 decision so as to resume its proactive recommendation of HPV vaccination. Unless Japan's governmental proactive recommendation for the HPV vaccine is soon resumed, the HPV infection rates will increase. As HPV is associated not only with cervical cancer, but also cancers of the vulva, vagina, anus, and oropharynx, it is predictable that there will eventually be large numbers of HPV-caused cancer morbidities and mortalities across Japan [25]. For the near foreseeable future, in the absence of any comprehensive national HPV vaccination program, our only hope to prevent a wave of cervical cancer will be by raising the cervical cancer examination rate. However, if the examination rate in Japan remains low as it is today, severe concerns about our future will be raised.

The MHLW, as well as our media and politicians, place great importance on supporting the vulnerable. They also try to

understand their situations and respond to their problems. For the last five years, MHLW has stood closest to those, claiming various adverse symptoms after inoculation, whether a causal relationship could be proven or not. The Nagoya's investigation into the association between the HPV vaccine and the reported adverse symptoms has shown that the rate of those adverse symptoms has not increased by HPV vaccine. However, no study can completely deny the possibility of rare adverse events after inoculation in individual cases. Apart from the diagnosis of adverse events in rare individual cases, the causal relationship between various symptoms and HPV vaccine is now widely considered to be negative. It is now time to steer in the direction of caring for young women who definitely have higher risks of cervical cancer and other easily preventable cancers with inaction on vaccination. If Japan's government reinstates a proactive recommendation of the HPV vaccine, Japan will become a health-conscious country.

We are now willing and able to provide serious medical treatment to any vaccinated or unvaccinated woman who presents with the purported adverse symptoms. As the medical clinicians on the front lines of prevention and treatments of cervical cancer, we expect that the MHLW will make a decision, based on an unbiased assessment, the perspective of scientific research to promote the health of individuals in Japan.

Acknowledgments

We would like to thank Dr. G.S. Buzard for his constructive criticism and editing our manuscript.

Funding

This paper was supported by funds from the Japan Agency for Medical Research and Development, grant number: 15ck0106103h0102.

Declaration of interest

Y. Ueda, A. Yagi, T Enomoto, M. Sekine, E. Myagi have received speakers fees from Merck Sharp and Dohme. E. Myagi has also received Honoria or speakers fees from Roche diagnostic, Japan Vaccine and grants from GlaxoSmithKline and Merck Sharp and Dohme. T. Kimmura has received research funding from Merck Sharp and Dohme (VT#55166). Y. Ueda has also received a research fund from Merck Sharp & Dohme (grant number J550703673). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Etsuko Miyagi http://orcid.org/0000-0002-1943-594X

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