



Commentary

Consensus statement from 17 relevant Japanese academic societies on the promotion of the human papillomavirus vaccine



Satoshi Iwata^a, Kenji Okada^b, Kei Kawana^{c,*}, on behalf of the Expert Council on Promotion of Vaccination¹

^a Department of Infectious Diseases, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

^b Section of Pediatrics, Department of Medicine, Division of Oral and Medical Management, Fukuoka Dental College, 2-15-1 Tamura, Sawara-ku, Fukuoka, Japan

^c Department of Obstetrics and Gynecology, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan

ARTICLE INFO

Article history:

Received 6 January 2017

Received in revised form 3 March 2017

Accepted 8 March 2017

Available online 18 March 2017

© 2017 Elsevier Ltd. All rights reserved.

In Japan, human papillomavirus (HPV) vaccines (bi-valent and quadri-valent) became part of the national immunization program following statutory procedures in April 2013. In response to media coverage regarding possible adverse events associated with this vaccine that caused confusion among potential Japanese recipients of the vaccine, the Japanese government (Ministry of Health, Labour, and Welfare in Japan) established an expert team to investigate and review the relevant data on HPV vaccine safety and efficacy and suspended proactive recommendation of its use in June 2013. In the nearly 4 intervening years since suspension of this recommendation, HPV vaccination in Japan has stagnated. Such stagnation is almost certainly related to limitations in access to accurate and up-to-date safety and efficacy data by the general public in Japan.

In light of several changes that have occurred in Japan since 2015, including an improved understanding of the rare adverse events associated with these vaccines, the establishment of a reporting and medical consultation and counseling system for these adverse events and the institution of a relief system for those that received vaccination and exhibited adverse health events, the Expert Council on Promotion of Vaccination (hereinafter referred to as “Council”), which consists of 17 Japanese academic societies

(including one associate society) with interests related to immunization and vaccination, would like to recommend renewed proactive support for the widespread use of the HPV vaccine. We base this recommendation on three main arguments.

First, efficacy data on these vaccines is now very strong. As of January 2016, 65 countries or 33.5% of the WHO membership have included HPV vaccines in their national immunization programs [1]. Several of these countries (e.g., Australia, USA, Denmark and Scotland) have reported that the incident rate of precancerous lesions of the uterine cervix has decreased by approximately 50% since institution of widespread immunization programs [2–5]. Drolet, et al. recently reported on a *meta*-analysis of HPV vaccine efficacy studies that HPV16/18 infections in girls aged 13–19 years old decreased by 68% in countries with vaccination coverage of at least 50% [6]. Excellent HPV vaccine efficacy has now been consistently demonstrated worldwide (reviewed in Ref. [6]). In stark contrast, the mortality rate from cervical cancer in Japan increased by 3.4% from 1995 to 2005 and is expected to increase by 5.9% from 2005 to 2015. This acceleration in disease burden is particularly evident among women aged 15–44 years [7].

Second, the frequency of adverse events associated with use of the HPV vaccine has now been extensively evaluated domestically and overseas. In a domestic survey in Japan, reports of alleged adverse events were made in 2584 cases out of a total of 8.9 million HPV vaccine doses (0.03% of total doses) given to 3.38 million persons (0.08% of total persons). Of those reporting adverse events, approximately 90% have had complete recovery. 186 persons (0.002% of total doses and 0.005% of total persons) are still receiving medical care related to adverse events (Table 1) [8]. In short, 2 people out of 100,000 administered doses have reported long-term health effects. Further safety data using re-investigations done by the European Medicine Agency (EMA) and a large scale re-examination of HPV vaccine safety profiles in France revealed no differ-

* Corresponding author.

E-mail address: kkawana-tyk@umin.org (K. Kawana).

¹ The Japanese Society for Vaccinology, The Japanese Association for Infectious Diseases, The Japanese Society of Child Health, Japan Society of Obstetrics and Gynecology, Japan Pediatric Society, Japan Pediatric Association, Japan Society for Well-being of Nursery-schoolers, The Japanese Respiratory Society, Japanese Society of Travel and Health, The Oto-Rhino-Laryngological Society of Japan, Japan Primary Care Association, Japanese Society for Infection Prevention and Control, The Japanese Society for Virology, Japanese Society for Bacteriology, Japanese Society of Clinical Virology, Japan Association of Obstetricians and Gynecologists, and Japan Society of Gynecologic Oncology (Associate society).

Table 1
Outcome of persons with AE (adverse events) after HPV vaccination in Japan.

| | No. of cases | % of immunized | % of confirmed cases |
|--|--------------|----------------|----------------------|
| Estimated no. of immunized | 3,380,000** | 100.00% | |
| Total no. of persons with AE | 2584 | 0.08% | |
| Total no. of confirmed cases on onset date and outcome | 1739 | 0.05% | 100.00% |
| Outcome | | | |
| Deaths* | 3 | 0.00% | 0.2% |
| Recovered | 1550 | 0.05% | 89.1% |
| Unrecovered | 186 | 0.005% | 10.7% |

* Suicide, neoplasm, cardiac diseases.

** 77% of immunized cases received bi-valent HPV vaccine.

ence in the occurrence rates of CRPS (Complex Regional Pain Syndrome), POTS (Postural Orthostatic Tachycardia Syndrome) or auto immune syndromes— all reported as potential vaccine-related issues in the media—between the vaccinated and unvaccinated cohorts [9].

Finally, Japan has now established specialized institutions and a robust nationwide medical consultation and counseling system for those who report symptoms after HPV vaccination. The Procedures for Medical Consultation was issued in Japan in August 2015 and has been distributed to all medical institutions that will be in charge of this clinical practice. The simultaneous creation of a relief system for those who have experienced purported vaccine-related adverse events further supports the viability of the present environment in Japan to support reinvigorated efforts to promote the prevention of HPV infection and cervical cancer.

During the past few years while proactive HPV vaccination promotion and programs have been suspended and cervical cancer rates have risen in Japan, the rates of pre-cancerous cervical lesions have decreased outside of Japan in areas with effective and widespread HPV vaccination policies. The World Health Organization (WHO) strongly recommends HPV vaccination from a public health standpoint. Further, WHO's Global Advisory Committee of Vaccine Safety (GACVS) has reaffirmed this opinion in its statement issued on Dec 17th, 2015, stating that “young women are being left vulnerable to HPV-related cancers that otherwise could be prevented” in areas without access to or promotion of HPV vaccine use. As noted previously by GACVS, policy decisions based on weak evidence leading to lack of use of safe and effective vaccines, can result in real harm” [10]. If proactive recommendation of HPV vaccination continues to be suspended in Japan, we are gravely concerned about the health and welfare of those women in our country that are not afforded the well-described cancer prevention benefits of these vaccines. It is the expert opinion of the Council that efficacy and safety data support nationwide proactive promotion of vaccination programs. We believe that the environment in Japan puts us in a good position to engage in such promotion and to support the small number of vaccinated people who report adverse events after vaccine administration. Part of this proactive promotion should include notification of those who may be interested in vaccination that data support efficacy and safety, that programs are now available for those with suspected adverse events to vaccination and that vaccination is now widely recommended. The Japan Society of Gynecologic Oncology is not a member of this

council, but the association agrees with the above recommendations and has therefore been listed in this document.

Conflicts of interest

None.

Acknowledgement

We thank to Prof. Danny J. Schust for his helpful suggestion during the editing of this manuscript.

References

- [1] Map production Immunization Vaccines and Biologicals (IVB), World Health Organization (WHO/IVB); <http://www.who.int/entity/immunization/monitoring_surveillance/VaccineIntroStatus.pptx?ua=1>; 11th January, 2016.
- [2] Baldur-Felskov B, Dehlendorff C, Junge J, Munk C, Kjaer SK. Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. *Cancer Causes Control* 2014;25:915–22.
- [3] Crowe E, Pandeya N, Brotherton JM, Dobson AJ, Kisely S, Lambert SB, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *BMJ* 2014;348:g1458.
- [4] Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer* 2014;111:1824–30.
- [5] Niccolai LM, Julian PJ, Meek JL, McBride V, Hadler JL, Sosa LE. Declining rates of high-grade cervical lesions in young women in Connecticut, 2008–2011. *Cancer Epidemiol Biomarkers Prev* 2013;22:1446–50.
- [6] Drolet M, Bénard É, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015;15:565–80.
- [7] Human Papillomavirus and Related Diseases Reports, Japan; The ICO Information Centre on HPV and Cancer: <<http://www.hpvcentre.net/summaryreport.php>>.
- [8] The 15th Vaccination Sub-committee Meeting: Investigative Committee on Adverse Reactions. Health Sciences Council, Ministry of Health, Labour, and Welfare, <<http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000097681.pdf>>; 17th September, 2015 [in Japanese].
- [9] European Medicine Agency (EMA). Pharmacovigilance Risk Assessment Committee (PRAC), Review concludes evidence does not support that HPV vaccines cause CRPS or POTS, <http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2015/11/WC500196309.pdf>; 5th November, 2015.
- [10] The World Health Organization: Global Advisory Committee on Vaccine safety Statement on Safety of HPV vaccines. <http://www.who.int/vaccine_safety/committee/GACVS_HPV_statement_17Dec2015.pdf?ua=1>; 17th December, 2015.