




RESEARCH ARTICLE



Survey of pediatricians concerning the human papillomavirus vaccine in Japan: Positive attitudes toward vaccination during the period of proactive recommendation being withheld

Megumi Kubota ^{a,b}, Kyoko Kondo ^c, Yasuo Tomiyoshi^a, and Wakaba Fukushima ^{b,d}

^aOsaka Pediatric Association, Osaka, Japan; ^bDepartment of Public Health, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; ^cResearch support platform, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; ^dResearch Center for Infectious Disease Sciences, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

ABSTRACT

In 2013, the human papillomavirus (HPV) vaccine was introduced as a national immunization program in Japan. However, because of a wide range of symptoms after vaccination, the Japanese Ministry of Health, Labor and Welfare decided to withhold proactive recommendations, a situation that has continued for more than eight years. During the withholding, absent any scientific or epidemiological evidence to support a relationship between HPV vaccines and symptoms, we surveyed pediatricians at Osaka Pediatric Association and analyzed the changing of attitudes in 2020 ($n = 200$) and 2021 ($n = 190$). A total of 44.5% respondents in 2020 and 67.9% in 2021 offered HPV vaccination to targets at the time the questionnaire was administered, indicating that the rate of pediatricians providing vaccines had increased significantly ($p < .001$). A total of 74.0% of respondents in 2020 and 77.9% in 2021 had a positive opinion of HPV vaccination ($p = .369$), and 64.3% in 2020 and 78.3% in 2021 were “not at all concerned or had almost no concern” about HPV vaccination ($p = .002$). These results suggest that, in general, most physicians who are primarily responsible for HPV vaccination in a given field had a positive attitude toward vaccination during the proactive recommendation having been withheld.

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Introduction

Cervical cancer is the fourth-most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020.¹ Human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Most sexually active women and men become infected at some point in their lives, some repeatedly. Cervical cancer is by far the most common HPV-related disease, and almost all cases of cervical cancer are thought to result from HPV infection.² In Japan, cervical cancer affects around 10,000 women every year, and the annual number of deaths from cervical cancer is reported to be around 2,800.³ The abnormal rate of cervical cancer screening in Japan demonstrates favorable changes with HPV vaccination and the positive impact of a period of high vaccination rates in Japan, albeit for a short time, is shown here.⁴ A nationwide case-control study in Japan showed a substantial risk reduction in abnormal cytology and cervical intraepithelial neoplasia (CIN) among women who did versus those who did not receive HPV vaccination.⁵ In England, a substantial reduction in cervical cancer and incidence of CIN3 in young women after the introduction of the HPV immunization program was observed, especially in individuals who were offered the vaccine at 12–13 years old.⁶

As the HPV vaccine is most effective when given before exposure to HPV, World Health Organization (WHO)

recommends vaccination for girls aged 9–14 years old, when most have not yet become sexually active. WHO reports that the HPV vaccine has been introduced into the national immunization program (NIP) in 120 countries around the world.⁷ Some countries have also started vaccinating boys, as it can prevent HPV-related cancers in men as well.⁸ In Australia, where both girls and boys are vaccinated and the vaccination rate remains above 80%, it is estimated that cervical cancer will become a rare disease within 10 years.⁹

Between 1990 and 2000, the Japanese vaccine policy did not keep pace with the world's standards, and for a long time, this was known as the “vaccine gap” and recognized as a major problem for the NIP in Japan.¹⁰ To address the vaccine gap issue, the HPV vaccine was added to the NIP in April 2013. Bivalent and quadrivalent vaccines were introduced into the NIP, and the targets were girls 12–16 years old. Both vaccines require three doses, with the standard schedule being 0, 1, and 6 months for the bivalent and 0, 2, and 6 months for the quadrivalent.¹¹ However, a wide range of symptoms after the vaccination was reported soon after its introduction, appearing daily in the media. The Japanese Ministry of Health, Labor, and Welfare (MHLW) therefore decided to withhold a proactive recommendation for the HPV vaccine,¹² a situation that has continued for more than 8 years, with vaccination coverage falling from over 70% to less than 1% for many years. The

WHO's Global Advisory Committee on Vaccine Safety has criticized that the Japanese government's policy decision on the HPV vaccine has not been based on scientific evidence.¹³

The symptoms reported following HPV vaccination, including chronic pain and movement disorders, were investigated in a nationwide epidemiological survey conducted by the Sobue Group of the Japanese MHLW^{14,15} and the Nagoya Study,¹⁶ but no scientific or epidemiological evidence has been presented to support a relationship between vaccination and these symptoms. In November 2021, the Japanese MHLW finally approved a policy to resume the proactive recommendation of the HPV vaccine based on the current evidence. The Committee reaffirmed the efficacy/effectiveness of the vaccine and noted that there was no particular safety concern.

During the period of withholding proactive recommendation in Japan, the vaccination rate rarely increased over 1%.^{17,18} Because most NIPs, including the HPV vaccine, are administered by pediatricians in Japan, the status of pediatricians' awareness of vaccination was considered important in order to increase the vaccination rate. However, only a survey of obstetricians and gynecologists on this point has been published in Japan and Nagase et al. pointed out the need to survey pediatricians who usually deliver HPV vaccines.^{19–22} To clarify pediatricians awareness, the prevalence of pediatricians actually recommending vaccination to the target population, and their changing attitudes during the absence of governmental recommendations, we conducted a survey among members of the Osaka Pediatric Association in January 2020 and June 2021.

Methods

We sent a survey invitation through an electrical questionnaire system via the Internet or fax to all members of the Osaka Pediatric Association in January 2020 and June 2021. The first survey was performed from January 23 to 2 February 2020. The number of dispatches was 700 (608 by e-mail and 92 by fax), and the number of responses was 200 (175 web responses and 25 fax responses). The second survey was performed from June 24 to 11 July 2021. The number of dispatches was 708 (647 by e-mail and 61 by fax), and the number of responses was 190 (179 web responses and 11 fax responses).

The questionnaires asked about respondents' pediatricians status and their intentions concerning HPV vaccination during the period of withholding proactive recommendations, how they acted when a child of the target age group visited their clinic, their general impression concerning the percentage of the public who accept HPV vaccination when recommended, whether or not they had any concerns about the HPV vaccine compared to other vaccines (and what kinds of concerns they held, if so), and whether or not they would recommend HPV vaccination to family members.

The questionnaire survey was primarily conducted as part of the annual project of the Osaka Pediatric Association. In the questionnaire, it was stated that the results would be presented in an academic paper or at a congress. Informed consent was waived because responses were collected anonymously. Subsequently, approval was obtained on 15 November 2021, from the Ethics Committee of Osaka City University (renamed

to Osaka Metropolitan University on 1 April 2022) to reanalyze and publish the results as research (approval number: 2021–182).

Statistical analysis

Since the survey was conducted among members of the Osaka Pediatric Association, no sample size calculations were made in advance. The chi-squared test or Fisher's exact test was performed to compare the baseline characteristics and changing attitudes between the two surveys. Because of the nature of the anonymous survey, the respondents to the two surveys were not necessarily the same, so paired tests were not applied. The SAS software program, version 9.4 (SAS Institute, Cary, NC, USA), was used for the analyses, and statistical significance was indicated by a *p*-value of <0.05.

Result

There were no significant differences between the respondents of the two surveys with regard to the baseline characteristics (Table 1). The response rates were 200/700 (28.6%) for the first survey and 190/708 (26.8%) for the second survey (*p* = .584). During the period of the two surveys, the MHLW's proactive recommendation withholding has continued, but the MHLW has requested in October 2020, for each municipality to be individually sent materials for the purpose of providing appropriate information on the HPV vaccine.

When asked how many HPV vaccinations they had provided in the last 6 months, the most common answer was "1 to 10" (73 [78.5%] in 2020 and 81 [59.6%] in 2021), followed by "11 to 30" (13 [14.0%] in 2020 and 40 [29.4%] in 2021), indicating that the number of vaccinations was still low (Table 2). The general impression of the percentage of people who accepted the HPV vaccine when it was recommended by their healthcare provider was "<20%" with 42 (55.3%) respondents in 2020 and 25 (29.1%) in 2021, "20%–40%" with 11 (14.5%) respondents in 2020 and 14 (16.3%) in 2021, and "40%–60%" with 9 (11.8%) of respondents in 2020 and 28 (32.6%) in 2021 (Table 2). Furthermore, 32.5% (2020) and 40.0% (2021) of respondents said, 'I try to recommend the vaccine,' and 34.0% (2020) and 38.4% (2021) said 'I don't prompt the vaccine, but I give it to those who ask for

Table 1. Baseline characteristics of respondents to the two surveys.

	1st (<i>n</i> = 200)	2nd (<i>n</i> = 190)	<i>p</i> -Value ^a
Age (years)			
30s	8 (4.0)	7 (3.7)	
40s	29 (14.5)	25 (13.2)	
50s	55 (27.5)	63 (33.2)	
60s	81 (40.5)	78 (41.1)	
Over 70s	27 (13.5)	17 (9.0)	0.561
Work status			
Employed physicians	51 (25.5)	55 (29.0)	
Owners of a clinic or a hospital	142 (71.0)	133 (70.0)	
Others	7 (3.5)	2 (1.1)	0.246

Data are expressed as *n* (%). ^a Chi-square test or Fisher's exact test was used as appropriate.

Table 2. Questionnaire items and distribution of the responses.

	1st	2nd	p-Value ^a	
Q1 “Which of the following best describes your HPV vaccination status and intentions since the withholding proactive recommendations?”				
• Vaccinations have continued unchanged thus far.	51	(25.5)	63	(33.2)
• Vaccinations were withheld for some time, but have recently been restarted.	38	(19.0)	66	(34.7)
• I have refrained from administering vaccinations since recommendation was withheld but will start again when proactive recommendation is resumed.	59	(29.5)	19	(10.0)
• I do not intend to administer vaccinations even if proactive recommendation is resumed.	9	(4.5)	10	(5.3)
• Others.	43	(21.5)	32	(16.8)
				<0.001
Q2 “What is the approximate number of vaccinations you have offered in the last six months?”				
• 1 to 10.	73	(78.5)	81	(59.6)
• 11 to 30.	13	(14.0)	40	(29.4)
• 31 to 50.	3	(3.2)	10	(7.4)
• 51 to 100.	4	(4.3)	4	(2.9)
• more than 101.	0	(0)	1	(0.7)
				0.013
Q3 “What do you do when girls in the target age group visit your outpatient clinic?”				
• I try to recommend the vaccine.	65	(32.5)	76	(40.0)
• I don’t prompt the vaccine, but I give it to those who ask for it.	68	(34.0)	73	(38.4)
• I don’t recommend the vaccine or administer it even if they ask.	28	(14.0)	16	(8.4)
• Others.	39	(19.5)	25	(13.2)
				0.068
Q4 “What is your general impression of the percentage of people who get the HPV vaccine when it is recommended by their healthcare provider?”				
• Less than 20%.	42	(55.3)	25	(29.1)
• Between 20% and 40%.	11	(14.5)	14	(16.3)
• Between 40% and 60%.	9	(11.8)	28	(32.6)
• Between 60% and 80%.	9	(11.8)	13	(15.1)

(Continued)

Table 2. (Continued).

	1st	2nd	p-Value ^a	
• More than 80%.	5	(6.6)	6	(7.0)
				0.005
Q5 “Do you have any concerns about the HPV vaccine compared to other vaccines?”				
• Not at all.	54	(27.1)	61	(32.3)
• Almost no concerns.	74	(37.2)	87	(46.0)
• Some concerns.	54	(27.1)	30	(15.9)
• Many concerns.	15	(7.5)	9	(4.8)
• Others.	2	(1.0)	2	(1.1)
				0.048
Q6 “What concerns do you have about HPV vaccination? ” (Multiple answers are acceptable)				
• Local symptoms, such as temporary pain and swelling at the injection site and anxiety about the vagus reflex.	37		20	
• Anxiety about a wide variety of symptoms, as repeatedly reported in the media.	46		24	
• Concerns about the effectiveness of the HPV vaccine.	5		2	
• Others.	9		5	
Q7 “Do you encourage family members who are eligible to get the HPV vaccine?”				
• Yes.	167	(83.5)	175	(92.1)
• No.	7	(3.5)	2	(1.1)
• No idea.	24	(12.0)	9	(4.7)
• Others.	2	(1.0)	4	(2.1)
				0.013

Data are expressed as n (%). ^a Chi-square test or Fisher’s exact test was used as appropriate.

it. (Table 2). A total of 89 (44.5%) respondents in 2020 and 129 (67.9%) in 2021 offered the HPV vaccine at the time the questionnaire was administered, indicating that the rate of responders who offered the HPV vaccine increased significantly over the study period ($p < .001$) (Table 3: [A] is defined as ‘Vaccinations have continued unchanged thus far.’ plus ‘Vaccinations were withheld for some time, but have recently been restarted again.’ in Q1, Table 2.). When additionally combined with the 59 respondents in 2020 and the 19 respondents in 2021 who stated that they would restart vaccination if given proactive recommendation, 74.0% of the respondents in 2020 and 77.9% in 2021 had a positive opinion regarding HPV vaccination ($p = .369$) (Table 3: [B] is defined as [A] plus ‘I have refrained from administering vaccinations since recommendation was withheld, however will start again when proactive recommendation is resumed.’ in Q1, Table 2.), and 128 (64.3%) in 2020 and 148 (78.3%) in 2021 were “not at all concerned or had almost no concern” about HPV vaccination,

Table 3. Attitude toward the HPV vaccine among pediatricians.

		<i>n</i>	(%)	<i>p</i> -Value ^a
[A] Currently administering the HPV vaccine. ^b	1st	89	(44.5)	<0.001
	2nd	129	(67.9)	
[B] Positive attitude toward the HPV vaccine. ^c	1st	148	(74.0)	0.369
	2nd	148	(77.9)	
[C] No or almost no concern about the HPV vaccine. ^d	1st	128	(64.3)	0.004
	2nd	148	(78.3)	

^aChi-square test or Fisher's exact test was used as appropriate.

^b[A] is defined as "Vaccinations have continued unchanged thus far." plus "Vaccinations were withheld for some time, but have recently been restarted." in Q1, Table 2.

^c[B] is defined as [A] plus "I have refrained from administering vaccinations since recommendation was withheld, however, I will start again when proactive recommendation is resumed." in Q1, Table 2.

^d[C] is defined as "Not at all." plus "Almost no concerns." in Q5, Table 2.

thus showing a significant difference between the surveys ($p = .004$) (Table 3: [C] is defined as "Not at all." plus "Almost no concerns." in Q5, Table 2). However a total of 69 respondents (34.6%) in 2020 and 39 (20.7%) in 2021 were "some concerns" or "many concerns" about vaccination, with the most common concerns being a wide variety of symptoms, as repeatedly reported in the media (46 respondents in 2020 and 24 respondents in 2021), and local symptoms, such as temporary pain and swelling at the injection site and anxiety about the vagus reflex (37 respondents in 2020 and 20 respondents in 2021) (Table 2). In addition, 167 (83.5%) in 2020 and 175 (92.1%) in 2021 said they would "encourage" HPV vaccination if they had a family member who was eligible ($p = .027$) (Table 2).

In free comments, the overwhelming majority of respondents wished for the resumption of proactive recommendations, with comments such as "I hope that it will be resumed as soon as possible (2020)," "It is strange that it has not been resumed when it has been proven that there is no difference in adverse events between Japan and other countries (2020)," "We want the 9-valent vaccine to become an NIP as soon as possible (2021)," and "If this situation continues, Japan will be the only country with high cervical cancer rates in 10 years (2021)." However, there were also a few cautious comments such as "Correct information needs to restart (2020)" and "There are still concerns about vaccination (2020)" or "Scientific data and human emotions are different things (2021)."

Discussion

To our knowledge, this is the first survey of pediatricians' attitudes to the HPV vaccine conducted during the period of withholding active recommendation in Japan. We found that 74.0% (2020) and 77.9% (2021) of pediatricians had positive attitudes toward vaccination. In 2014, 2017, and 2019, Ueda et al. sent an anonymous questionnaire to 575, 567, and 573 physicians, respectively who had trained in the department of obstetrics and gynecology at Osaka University Hospital and its affiliated hospitals.^{18–22} They received responses from approximately half of them: 264 (2014), 259 (2017), and 264 (2019). According to the results, respondents who answered, "the government should resume active recommendation" increased from 61.0% in 2014 to 73.6% in 2017 and 83.3% in 2019; those who answered, "I recommend the HPV vaccine to my teenage patients" increased from 65.2% in 2014 to 70.1% in 2017 and 84.6% in 2019; and

those who answered, "I have vaccinated my teenage daughter" increased from 0% in 2014 to 16.1% in 2017 and 36.7% in 2019. These results suggest that, in general, most physicians in fields who are primarily responsible for HPV vaccination like pediatricians and obstetricians/gynecologists, had a positive attitude toward vaccination. In addition, these attitudes are not only related to the HPV vaccine, but also to the question of how we pediatricians can prevent Vaccine Preventable Disease (VPD) with the vaccines. From this perspective, it is necessary to discuss effective ways to recommend HPV vaccine as a VPD.

Pediatricians have more contact with teenagers than physicians in other fields, so they need to be efficient in recommending the HPV vaccine when targets visit their clinics and hospitals. A survey in the U.S. determined the prevalence of physician recommendations for HPV vaccination in early, middle, and late adolescent and young adult female patients by physician specialty. A total of 1013 physicians (500 family physicians, 287 pediatricians, and 226 obstetricians/gynecologists) responded, with pediatricians being the most likely to 'always' recommend the HPV vaccine across all age groups ($P < .001$).²³ In other article, while HPV vaccine coverage remains low in the U.S., despite its inclusion as an NIP, there is research on how vaccination coverage relates to communication between healthcare professionals showing that parents place the highest importance on the doctor's explanation in their decision-making process regarding whether or not to have their child vaccinated against HPV. It also concluded that improved communication among healthcare professionals is needed in order to effectively recommend the vaccine.²⁴

Through our survey, physicians who reported having concerns about the HPV vaccine were most frequently concerned about the wide variety of symptoms that were repeatedly reported in the media. In fact, amidst the sharp drop in vaccination coverage during the period of withholding proactive recommendation in Japan, we were reminded of how difficult it is to communicate scientifically valid messages to teenagers and their parents. No matter how legitimate the scientific arguments, public opinion is always influenced by more emotive messages. There was a study conducted in the U.S. in 2019²⁵ that observed how the HPV vaccine was covered on Instagram, a social media platform that is rapidly spreading among young people. They searched for "#HPV," "#HPVVaccine," and "#Gardasil" and found that of the 360 valid posts, 55.8% included positive messages about vaccine, while 42.2% included

negative messages about the vaccine. The number of “Likes” and “Agreements” with these posts was 86 for opponents compared to 24 for proponents. In contrast to the narratives of the opponents, who often expressed personal beliefs in an emotional way, the proponents were more likely to post simple content about their experiences with the vaccine and rarely provided detailed information about vaccination or lifelong cancer prevention.²⁶ As described in this article,²⁶ social media is an effective tool for communicating messages to teenagers not only about the HPV vaccine, but also about vaccines in general and medical information, but we must also be aware of the risks of spreading misinformation. We have a mission to continue to deliver correct information based on scientific evidence, and we need to be more specific in the way we communicate and encourage teenagers and their parents to think independently.

Japan has had issues with the vaccine gap for long time, but recently it is recognized as finally approaching the global standard.¹⁰ However, this withholding of proactive recommendation of the HPV vaccine has once again brought to the surface the issue of the Japanese policies toward vaccines. Although this HPV vaccine has now returned to the regular NIP program after more than eight years, we hope that this experience will be one of the materials to establish robust vaccine policies in Japan in the future. These surveys were initially conducted to investigate pediatricians’ attitudes toward the HPV vaccine in Japan, but we believe that this will provide material for reconsider pediatricians,’ parents,’ and children’s attitudes toward current vaccines, including the COVID-19 vaccines, as well as solutions for the recent increase in vaccine hesitancy.

This survey has two limitations. First, it was conducted among members of the Osaka Pediatric Association and not throughout Japan, so it is not representative of the attitudes of pediatricians nationally, although Osaka Pediatric Association is a general incorporated association representing pediatrics in Osaka Prefecture and has the largest number of members among all pediatric associations in Japan. Second, the survey was conducted anonymously, and it was not possible to identify the individuals who responded to the first and second surveys. Although the anonymous nature of the survey is considered to elicit honest opinions, it was not possible to track changes in attitudes on an individual basis. The next survey should consider a research design to address this limitation and extract changes in attitudes among a broader range of subjects and individuals.

Conclusions

The present study explored pediatricians’ awareness of the HPV vaccination during the period of proactive recommendation being withheld in Japan. Our survey revealed that most pediatricians had a positive attitude toward HPV vaccination, despite proactive recommendation having been continuously withheld for more than eight years.

From April 2022, girls between 12 and 16 years old were able to receive the HPV vaccine with proactive recommendation by the Japanese MHLW, and women who had not been able to receive the HPV vaccine at the recommended age while

it was not properly recommended by the government were given opportunities to do so, such as the chance to receive immunization promptly free of charge.

As the surveys revealed pediatricians’ attitudes toward HPV vaccination, we expect that the findings of these surveys will help to clarify the importance of addressing all VPD vaccines with a scientific rationale.

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Author contributions

Conceptualization, M.K.; formal analysis, M.K., and K.K.; investigation, M.K.; data curation, M.K.; writing – original draft preparation, M.K.; writing – review and editing, K.K., Y.T., and W.F.; supervision, W.F., and K.K.; project administration, M.K. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Osaka City University (protocol code 2021–182 on 15 November 2021). Osaka City University was renamed Osaka Metropolitan University on April 1, 2022.

Informed consent statement

Not applicable because responses in the survey were collected anonymously.

Disclosure statement

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ORCID

Megumi Kubota  <http://orcid.org/0000-0002-1169-623X>

Kyoko Kondo  <http://orcid.org/0000-0003-1567-0667>

Wakaba Fukushima  <http://orcid.org/0000-0002-3666-6942>

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