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Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan

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ABSTRACT

Objective In 2013, the Japanese government suspended its proactive recommendation of the human papillomavirus (HPV) vaccine (HPVv). The vaccination rate of the HPVv declined to <1% in 2014–2015. Previous studies have shown that the recommendation by a physician affects a recipient's decision to receive a vaccine, and physicians' accurate knowledge about vaccination is important to increase vaccine administration. This study aimed to evaluate the association between physicians' vaccination knowledge and the administration or recommendation of the HPVv among primary care physicians (PCPs) without proactive recommendation from the government in Japan.

Design Cross-sectional study.

Setting In 2019, a web-based, self-administered questionnaire was distributed among physicians of the Japan Primary Care Association (JPCA) on the official mailing list.

Participants Physicians who were not part of the mailing list, junior residents, those living outside Japan, those employed in a non-clinical setting, and those with missing/insufficient data were excluded.

Primary and secondary outcome measures The outcome of this study was the association between PCPs' vaccination knowledge and the administration or recommendation of the HPV vaccine. We obtained information on physicians' background and vaccination quiz scores and performed logistic regression analysis to estimate the adjusted odds ratios (AORs).

Results We received responses from 1,084 PCPs (20.1%) and enrolled 981 participants in the analysis. PCPs with a higher score on the vaccination quiz were significantly more likely to administer the HPVv for routine and voluntary vaccination (AOR 2.28, 95% confidence interval [CI] 1.58–3.28; AOR 2.71, 95% CI 1.81–4.04, respectively) and recommend the HPVv for routine and voluntary vaccination than PCPs with a lower score (AOR 2.17, 95% CI 1.62–2.92; AOR 1.88, 95% CI 1.32–2.67, respectively).

Conclusions We identified a positive association between the administration or recommendation of the HPVv and PCPs with accurate vaccination knowledge.

Strengths and limitations of this study

- This is the first study to focus on the association between primary care physicians' (PCPs) vaccination knowledge and the administration or recommendation of the HPV vaccine without proactive recommendation from the government in Japan.
- To explore this association, multivariable logistic regression analysis was performed with 10 possible confounding factors including the physicians' postgraduate year, the percentage of paediatric patients, and information resources about vaccination.
- One limitation of this study was its potential selection bias, which was due to the PCPs' voluntary participation in the survey.
- Furthermore, the effects of vaccine hesitancy from parents or the media on the PCPs were not

evaluated.

Data availability statement

Data are available upon reasonable request.

Keywords: HPV vaccine; primary care physicians; administration; recommendation; vaccination

INTRODUCTION

The World Health Organization (WHO) recognises the importance of cervical cancer and other human papillomavirus (HPV)-related diseases as global public health problems and recommends that HPV vaccines (HPVv) should be included in national immunization programmes.(1) In Japan, the HPVv was introduced in 2009 as a voluntary vaccination without a recommendation or funding from the Government of Japan.(2, 3) Since 2010, an urgent promotional campaign for vaccination has been conducted by the Ministry of Health, Labour and Welfare (MHLW), and the Government of Japan implemented subsidies to local governments for HPVv fees.(2, 3) This campaign was successful, and the vaccination rate of HPVv reached 70–80% of the targeted group, young girls, in 2012.(3, 4, 5, 6) In April 2013, HPV vaccination for 12- to 16-year-old girls was initiated as part of the routine vaccination program.(3, 7) However, the media widely reported an “adverse event” of HPV vaccination in young girls, that gave rise to social distrust, and vaccine hesitancy of the HPVv arose.(3, 7, 8) Consequently, the MHLW suspended proactive recommendation of HPV vaccination in June 2013,(7, 9) and the HPV vaccination rate declined to less than 1% in 2014–2015.(5, 6)

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data of HPVv from 2008 to 2015, and the committee considered HPVv to be extremely safe(10). In 2017, GACVS expressed concerns regarding the situation in Japan, stating that the mortality rate from cervical cancer was expected to increase because HPVv was not proactively recommended.(10) In 2018, Suzuki et al. reported that there was no association between HPVv and adverse post-vaccination

symptoms in Nagoya, Japan.(11) However, the MHLW still continued the suspension of proactive recommendation of HPV vaccination as of 2019. Vaccine hesitancy has occurred in other countries as well, and the WHO has identified vaccine hesitancy one of 10 threats to global health in 2019.(12)

Previous studies have shown that vaccine recommendation by a physician affects the recipient's decision in receiving a vaccine.(13, 14, 15, 16, 17, 18) Physicians' accurate knowledge about vaccination is important to increase vaccine administration or recommendation rates.(19, 20, 21) In Japan, the HPVv is administered not only by paediatricians, obstetricians, and gynaecologists (OBGYNs), but also by primary care physicians (PCPs).(22, 23) A nationwide survey on practices and attitudes towards vaccination among PCPs was conducted in Japan in 2012,(22, 23) when the proportion of PCPs who were administering and actively recommending HPV vaccination was 58.3% and 46.5%, respectively.(22) A significant association between PCPs' awareness of public subsidies for the HPVv and recommendations for HPV vaccination was reported.(23)

As previously indicated, the government vaccination policy for the HPVv changed after that survey(22, 23) and it was expected that these proportions would also change, but the current fraction of the PCPs that either administer or recommend the HPVv and the association between PCPs' knowledge about vaccination and their attitude towards HPVv in Japan is unknown. Therefore, this study aimed to evaluate the association between PCPs' knowledge about vaccination and the administration or recommendation of the HPVv without proactive recommendation from the government.

METHODS

Study design, setting, and population

This study used a cross-sectional design with data collected using a web-based, self-administered questionnaire conducted by the Preventive Medicine and Health Promotion Committee Vaccine Team of the Japan Primary Care Association (JPCA), which is the largest academic association for PCPs in Japan. The majority of the JPCA physicians were internists working as PCPs at clinics or hospitals. The survey was conducted from March to June 2019 and included only JPCA physician members. The inclusion criteria were physicians who were JPCA members using the official mailing list for only JPCA members. PCPs who were junior residents within 2 years after graduation from medical school were excluded, as this group cannot administer outpatient vaccinations without the supervision of attending physicians. Further exclusion criteria included PCPs who were living outside Japan, retired, employed in a non-clinical setting, and those with missing data.

Patient and public statement

Patient and/or the public were not involved in this study.

Questionnaire

Questionnaire items were revised from previous questionnaires administered by the Preventive Medicine and Health Promotion Committee Vaccine Team of JPCA,(22, 23) and were distributed through the online mailing list of JPCA members. The questionnaire was self-conducted and anonymous, collecting data on the participating physicians' baseline characteristics, such as sex, career after graduation, experience raising children, provision of daily paediatric medical service, provision of medical services at their main working facility, and vaccination quiz scores.

Main outcome

The primary outcome of this study was the association between PCPs' knowledge about vaccines and administration of the HPVv for routine and voluntary vaccination, respectively. As of 2019, the target group for HPV vaccination is as follows: routine vaccination, bivalent and quadrivalent HPVv for 12–16-year-old females; voluntary vaccination, bivalent HPVv for ≥10-year-old females and quadrivalent HPVv for ≥9-year-old females.(24) The PCPs were asked the following yes/no question: "Do you administer routine vaccination of the human papillomavirus vaccine for children?" The secondary outcome of this study was the association between PCPs' knowledge about the vaccine and PCPs' recommendation of routine vaccination for HPV for children. The respondents were asked, "How do you recommend routine vaccination for HPV for children?" The response options, on a Likert-type scale, were "Actively recommend," "Recommend occasionally," "No opinion," "Not actively recommend," and "Not recommend." An answer of "Actively

recommend" was defined as "recommending behaviour," which is a more positive behaviour.(14) Furthermore, "Recommend occasionally," "No opinion," "Not actively recommend," and "Not recommend" were defined as "no recommending behaviour."

Main factor

The main factor was PCPs' knowledge of vaccination, measured by the score on a vaccination quiz. The quiz was created by the Preventive Medicine and Health Promotion Committee Vaccine Team of the JPCA using the Delphi method.(25) The quiz comprised six general vaccine questions covering Japanese vaccination affairs, including a question on the HPVv. The quiz score was the number of correct answers to each of the six questions: 0–6 points. To obtain a binary variable, we designated scores above the average as high, and those below the average as low. High or low vaccination quiz score was considered as the independent variable.

Possible confounding factors

Possible confounding factors included the physician's sex, postgraduate year (3–5, 6–10, 11–20, 21–30, 31–40, and ≥41 years), possession of any specialist qualifications including primary care, main practice category (primary care or not), practice setting (university hospital or general hospital, other hospital, clinic, others; university, research institution, government, health organization, etc.), the proportion of paediatric patients (number of paediatric patients with respect to the total patient

population) that was high (≥10%) or low (<10%), main working area as an administrative unit of the local government in an urban area (≥50,000 people) or not, experience as a kindergarten or school physician, experience raising children as a parent, and information resources about vaccinations (government, academic, commercial,(26) online professional community such as website / Facebook group / Twitter / JPCA mailing list,(27) and none).

Statistical analysis

We performed univariate and multivariate logistic regression analysis to estimate the odds ratios, the adjusted odds ratios (AORs), and 95% confidence intervals (CIs), using binary variables for the main outcome. We investigated the association between knowledge of vaccination among PCPs and their administration or recommendations for the HPVv.

Multiple logistic regression analysis was performed, adjusting for confounding factors as listed above: physician's sex, postgraduate year, possession of any specialist qualifications, including primary care, main practice category, practice setting, a high or low proportion of paediatric patients, experience raising children as a parent, and information resources about vaccinations.

We conducted sensitivity analysis to inspect each variation only for HPVv knowledge (correct or incorrect) rather than for the total quiz score. We used penalized maximum likelihood logistic regression for the analyses when any confounding factors were completely separated.(28)

The analysis participants were selected after excluding participants with missing data for the main outcome, main factor, and possible confounders (mentioned above).

All statistical analyses used two-tailed tests of significance, with significance set at $p < 0.05$.

Analyses were performed using Stata/SE 14.2 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study flow and demographics

Among the 10,470 physician members of the JPCA, 5,075 who did not subscribe to the mailing list were excluded. We received responses from 1,084 of 5,395 PCPs, for a response rate of 20.1%. The respondents were from all 47 prefectures of Japan. An additional 103 participants were excluded because they lived outside Japan, performed nonclinical work, or had missing data. The analysis included 981 participants (Figure 1). The median (interquartile range) score for the vaccination quiz was 4 (range, 2–5) points. The minimum and maximum scores were 0 and 6 points, respectively, and the mean (standard deviation) score was 3.47 (1.68) points. To obtain a binary variable, scores of ≥4 were designated as high and scores of ≤3 as low. Baseline characteristics showed that 739 (75.3%) participants were men, 358 (36.5%) had been working for 11–20 years after graduation, 420 (42.8%) were working in clinics, 719 (73.3%) were working in the urban areas, and 283 (28.9%) were working in a clinical setting where the proportion of paediatric patients was ≥10% (Table 1).

Factors associated with the administration of the HPVv for routine vaccination

We found that 229 PCPs (23.3%) administered the HPVv for routine vaccination. PCPs with higher vaccination quiz scores were significantly more likely to administer the HPVv for routine vaccination than those with lower scores (AOR 2.28, 95% CI 1.58–3.28, $p < 0.001$) (Table 2). There was also a positive association between administration of routine HPV vaccination and PCPs who worked at clinics (AOR 2.64, 95% CI 1.60–4.36, $p < 0.001$), those who had a higher proportion of paediatric patients (AOR 1.78, 95% CI 1.24–2.55, $p = 0.002$), and those who had experience as a kindergarten or school physician (AOR 2.12, 95% CI 1.45–3.10, $p < 0.001$).

Factors associated with the administration of the HPVv for voluntary vaccination

We found that 175 PCPs (17.8%) administered the HPVv for voluntary vaccination. PCPs with higher scores on the vaccination quiz were significantly more likely to administer the HPVv for voluntary vaccination than those with lower scores (AOR 2.71, 95% CI 1.81–4.04, $p < 0.001$) (Table 3). There was also a positive association between administration of voluntary HPV vaccination and PCPs who acquired information from governments (AOR 1.90, 95% CI 1.17–3.08, $p = 0.009$) and those who had social network service or mailing list from an individual or group of medical service providers (AOR 1.82, 95% CI 1.25–2.64, $p = 0.002$).

Factors associated with the recommendation of the HPVv for routine vaccination

The classification of PCPs recommendation of the HPVv for routine vaccination showed that 408 PCPs (41.6%) "Actively recommend," 319 (32.5%) "Recommend occasionally," 181 (18.5%) "No opinion," 49 (5.0%) "Not actively recommend," and 24 (2.5%) "Not recommend." PCPs with higher scores on the vaccination quiz were significantly more likely to recommend the HPVv for routine vaccination than those with lower scores (AOR 2.17, 95% CI 1.62–2.92; $p < 0.001$) (Table 4). However, there was a negative association between recommending routine HPV vaccination and PCPs who worked at other hospitals (AOR 0.69, 95% CI 0.48–1.00, $p = 0.048$) and clinics (AOR 0.67, 95% CI 0.46–0.98, $p = 0.041$), those who had a higher proportion of paediatric patients (AOR 0.50, 95% CI 0.36–0.70, $p < 0.001$), and those who acquired information from government sources (AOR 0.69, 95% CI 0.50–0.96, $p = 0.026$).

Factors associated with recommendation of the HPVv for voluntary vaccination

The classification of PCPs recommendation of the HPVv for voluntary vaccination showed: 216 PCPs "Actively recommend" (22.0%), 358 "Recommend occasionally" (36.5%), 288 "No opinion" (29.4%), 75 "Not actively recommend" (7.7%), and 44 "Not recommend" (4.5%).

PCPs with higher vaccination quiz scores were significantly more likely to recommend the HPVv for voluntary vaccination than those with low scores (AOR 1.88, 95% CI 1.32–2.67, $p < 0.001$) (Table 5). There was also a positive association between recommendation of voluntary HPV

vaccination and PCPs who were male (AOR 1.67, 95% CI 1.12–2.49, $p = 0.012$) and those who had social network service or mailing list for medical service from an individual or group of providers (AOR 1.56, 95% CI 1.09–2.24, $p = 0.016$). However, there was a negative association between recommendation of voluntary HPV vaccination and PCPs who had a higher proportion of paediatric patients (AOR 0.52, 95% CI, 0.34–0.78, $p = 0.002$) and those who had experience raising children (AOR 0.67, 95% CI 0.45–1.00, $p = 0.049$).

Sensitivity analysis

PCPs with correct answers to the HPV vaccination quiz were significantly more likely to administer the HPVv than those with incorrect answers for routine vaccination (AOR 2.06, 95% CI 1.38–3.09, $p < 0.001$) and for voluntary vaccination (AOR 2.16, 95% CI 1.39–3.34, $p = 0.001$).

PCPs with correct answers on the HPV vaccination quiz were significantly more likely to recommend HPV vaccination than those with incorrect answers for routine vaccination (AOR 1.51, 95% CI 1.12–2.04, $p = 0.006$) and for voluntary vaccination (AOR 1.53, 95% CI 1.07–2.19, $p = 0.02$).

DISCUSSION

This is the first study to focus on the association between PCPs' knowledge of vaccination and their practice or attitude toward the HPVv without proactive recommendation from the government in

Japan. We found positive associations between PCPs' vaccination knowledge and the administration or recommendation of the HPVv for routine and voluntary vaccination. We also found positive associations between different information resources and administration or recommendations of voluntary HPV vaccination.

As of 2019, the proportion of PCPs who administered or actively recommended the HPVv for routine vaccination (23.3% and 41.6%, respectively) was the lowest compared with other routine vaccines (39.5–95.5% and 74.5–92.0%, respectively) in Japan.(29) Compared to a previous study in 2012,(22) the proportion of HPVv administration among PCPs decreased from 58.3% for voluntary vaccination only(22) to 23.3% for routine vaccination and 17.8% for voluntary vaccination, and the proportion of HPVv recommendation among PCPs decreased from 46.5% for voluntary vaccination only(22) to 41.6% for routine vaccination and 22.0% for voluntary vaccination. A study conducted among paediatricians in Osaka, Japan, in 2020 and 2021 reported that the proportion of paediatricians who administered or actively recommended the HPVv for routine vaccination was 44.5% and 32.5% in 2020 and 67.9% and 40% in 2021, respectively.(30) In addition, a study conducted among OBGYNs in Osaka, Japan, reported that the proportion of OBGYNs who recommended the HPVv for teenagers was 70.1% in 2017(3) and 84.6% in 2019.(31) As of 2018, the proportion of family physicians and paediatricians in the United States who administered the HPVv was 84.1% and 95.3%, respectively,(32) and the proportion who strongly recommended the HPVv was 72–90% and 85–99% (11- to 12-year-old, 13- to 14-year-old, and ≥15 years female patients),

respectively.(32) Our study revealed that in Japan, PCPs may administer routine HPV vaccination less than paediatricians,(30) and PCPs might actively recommend routine HPV vaccination more than paediatricians,(30) but less than OBGYNs.(3) In addition, our study shows that Japanese PCPs might administer or recommend the HPVv less than family physicians in the United States.(32)

Our study revealed the association between PCPs' accurate knowledge of vaccination and their recommendation for HPV vaccination. In addition, as a sensitivity analysis, our study showed that physicians with accurate knowledge of HPV vaccination were likely to recommend the HPVv. A systematic review published in 2021 that examined healthcare providers' vaccine perceptions, knowledge, and recommendations to patients, including 96 papers from 34 countries, showed that recommendations were positively associated with healthcare provider knowledge and experience, beliefs about disease risk, and perceptions of vaccine safety, necessity, and efficacy.(33) The results of our study are consistent with this systematic review.(33) In Lebanon, where HPVv is not included in their national routine vaccination schedule as of 2017, physicians practicing in OB-GYN, paediatrics, family medicine, and infectious diseases with higher scores of knowledge about HPV and HPVv recommend the HPVv more often (AOR 3.4).(34) Further, in the United States, higher rates of HPV vaccination completion of three doses (IRR 1.28) were observed among primary care clinicians including family medicine physicians, general paediatricians, and family and paediatric nurse-practitioners with greater knowledge of HPV and the HPVv (35). Our results also support these findings. Another study investigating the association between PCPs' knowledge of vaccination

and the administration or recommendation of voluntary mumps vaccination for adults showed the same positive associations.(36)

Information resources from social network services or mailing lists from medical service providers seem to be positively associated with the administration or recommendation of voluntary HPV vaccination. This might be because PCPs use virtual communities as valuable knowledge portals for sourcing clinically relevant information(37) and could be interested in understanding how and why other physicians recommend and administer vaccination.(21, 36) Government information resources were positively associated with the administration of voluntary HPVv; however, it was negatively associated with the recommendation of routine HPV vaccination. As of 2019, the suspension of proactive recommendation for routine HPV vaccination by the MHLW was still implemented. This suspension was not meant to suspend routine vaccination, although some PCPs might have misinterpreted it as suspension of routine vaccination. Therefore, PCPs who know this policy from government information might administer voluntary instead of routine HPV vaccination, and might not recommend routine HPV vaccination. Alternatively, PCPs who know of the suspension might lose their confidence to recommend the HPVv. A previous study reported that the lack of government recommendations was one of the barriers for PCPs to recommend vaccination.(22) In November 2021, the MHLW ended this suspension and restarted “proactive recommendation,” targeting girls born in or after the fiscal year (FY) 2006, beginning in April 2022(38), and started “catch-up vaccinations” for 3 years, from April 2022 to March 2025, for females born in FY1997 to

FY2005 who became eligible for routine HPV vaccination, while they might have missed the opportunity to receive the vaccination because of the suspension.(39, 40) The results of our study suggest that providing accurate knowledge and information about HPV vaccination to PCPs might make more PCPs administer and recommend the HPVv, which might increase the vaccination rate. The JPCA vaccine team provides information about vaccination through websites(41) and regular onsite and online vaccine seminars for physicians.(42)

Our study also shows that PCPs who are working at clinics, providing daily paediatric medical services (more than 10% of total patients), and have experience as kindergarten or school physicians tend to administer routine HPV vaccination (Table 2). The target population for routine HPV vaccination is 12- to 16-year-old girls, and PCPs with this experience might understand the need for routine vaccination; therefore, they might be more likely to administer the vaccination. In contrast, PCPs working at clinics or other hospitals providing daily paediatric medical services (more than 10% of total patients) were less likely to recommend routine HPV vaccination (Table 4). In addition, PCPs who provide daily paediatric medical services (more than 10% of total patients) and had experience raising children tended to be less likely to recommend voluntary HPV vaccination (Table 5). These results suggest that PCPs who had more opportunity to provide medical service to 12- to 16-year-old girls might have less confidence to recommend the HPVv during the suspension of proactive recommendation by the MHLW or might be more affected by anxiousness or hesitancy of the parents.(18, 22, 43)

This study has some limitations. First, there was a potential selection bias due to the low response rate. PCPs who more actively promoted vaccination may have been more likely to respond, and the actual proportion of PCPs' administration or recommendation for the HPVv may be lower. Second, our study did not include voluntary vaccination for HPVv in men. In Japan, as of 2019, the target group for both routine and voluntary HPV vaccination was only women, although, in 2020, men were approved for voluntary vaccination with the quadrivalent HPVv. Third, our study did not evaluate 9-valent HPVv for voluntary vaccination, although, in 2021, the 9-valent HPVv was approved for voluntary vaccination(24) and will be approved for routine vaccination from April 2023.(44) In future studies, men should also be targeted in addition to women while performing such surveys, and 9-valent HPVv should be included as a study subject. Fourth, we did not evaluate the effects of vaccine hesitancy from the parents or mainstream media and social media on the PCPs.(43) Including the effect of vaccine hesitancy as one of exposures in the future studies would be useful. Fifth, we did not evaluate the effects of unknown confounding factors, which is a general limitation of observational studies. Finally, although the study participants were physician members of the JPCA, the largest society for PCPs in Japan, generalisability of the results to PCPs outside of Japan was unclear. The vaccination policy for the HPVv in Japan(39) changed after this study was conducted, and further surveys are needed to assess the current situation of HPV vaccination and attitude among PCPs.

CONCLUSIONS

We revealed a positive association between PCPs' vaccine knowledge and the administration or recommendation of routine and voluntary HPV vaccination without proactive recommendation from the government. Several factors influence PCP's perception of HPV vaccinations, ultimately affecting public healthcare. Our results suggest that providing more knowledge about vaccination to PCPs may increase their likelihood to administer or recommend the HPVv, thereby improving vaccination rates. Moreover, the results of our study can be applied to other countries with similar vaccination situations, such as those with vaccine hesitancy and disagreements between the scientific community and governments on vaccine policy.(8, 45)

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

We obtained written informed consent from all participants before conducting the survey.

Ethics approval

The study protocol was approved by the Institutional Review Board of XXX.

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Contributors: All authors declare they have contributed to this article. YS conducted the questionnaire, designed and implemented the survey, and performed analysis, interpretation of the data, wrote the draft manuscript, and performed critical revisions. JT conducted the questionnaire, designed and implemented the survey, interpretation of the data, and performed critical revisions. RS, KN, YN, HC, TK and AM conducted the questionnaire, interpretation of the data, and critical revisions. MM interpretation of the data, and critical revisions. TO and TS arranged for delivering the questionnaire, and critical revisions. All authors read and approved this manuscript version for submission.

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TABLES

TABLE 1 Characteristics of the participants

	Participants, n=981	Responders, n=1084
	n (%)	n (%)
Sex: male	739 (75.3), Missing 0	749 (69.1), Missing 88 (8.1)
Postgraduate year (y)	Missing 0	Missing 88 (8.1)
3–5	92 (9.4)	92 (8.5)
6–10	178 (18.1)	181 (16.7)
11–20	358 (36.5)	364 (33.6)
21–30	193 (19.7)	197 (18.2)
31–40	134 (13.7)	135 (12.5)
≥41	26 (2.7)	27 (2.5)
Main practice category: primary care	697 (71.1), Missing 0	705 (65.0), Missing 90 (8.3)
Practice setting	Missing 6 (0.6)	Missing 95 (8.8)
University hospital or general hospital	281 (28.6)	283 (26.1)
Other hospital	254 (25.9)	255 (23.5)
Clinic	420 (42.8)	426 (39.3)
Others (University, research institution, government, health organization, etc.)	20 (2.0)	25 (2.3)
Providing daily paediatric medical service (≥ 10% of total patients)	283 (28.9), Missing 0	291 (26.9), Missing 88 (8.1)
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	719 (73.3), Missing 2 (0.2)	733 (67.6), Missing 90 (8.3)
Experience of kindergarten or school physician	474 (48.3), Missing 0	478 (44.1), Missing 88 (8.1)
Experience raising children	721 (73.5), Missing 0	734 (67.7), Missing 88 (8.1)

Main practice category: primary care: Answered main practice category as family physician or general practitioner or hospitalist/general physician

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TABLE 2 Factors associated with administration of HPV vaccine for routine vaccination

	PCPs who administer HPV vaccine, n=229 (23.3%)	PCPs who do not administer HPV vaccine, n=752 (76.7%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio* (95% CI), n=977	*p*-value
Factors	n (%)	n (%)	n (%)		n (%)	
High scores in vaccination quiz (4–6 points)	172 (75.1)	339 (45.1)	3.68 (2.64–5.12)	<0.001	2.28 (1.58–3.28)	<0.001
Sex: male	178 (77.7)	561 (74.6)	1.19 (0.84–1.69)	0.380	1.11 (0.75–1.65)	0.600
Postgraduate year (y)						
3–5	14 (6.1)	78 (10.4)	Reference		Reference	
6–10	28 (12.2)	150 (20.0)	1.04 (0.52–2.09)	0.910	0.48 (0.20–1.18)	0.110
11–20	95 (41.5)	263 (35.0)	2.01 (1.09–3.72)	0.026	0.83 (0.34–2.02)	0.680
21–30	51 (22.3)	142 (18.9)	2.00 (1.04–3.84)	0.037	0.91 (0.37–2.27)	0.850
31–40	34 (14.9)	100 (13.3)	1.89 (0.95–3.77)	0.069	0.80 (0.32–1.99)	0.630
≥41	7 (3.1)	19 (2.5)	2.05 (0.73–5.79)	0.170	0.79 (0.23–2.67)	0.700
Position of any specialist qualification	201 (87.8)	643 (85.6)	1.21 (0.77–1.88)	0.410	1.04 (0.57–1.89)	0.890
Main practice category: primary care	183 (79.9)	514 (68.4)	1.84 (1.29–2.63)	0.001	1.18 (0.74–1.88)	0.500
Practice setting						
University hospital or general hospital	28 (12.2)	253 (33.8)	Reference		Reference	
Other hospital	35 (15.3)	219 (29.2)	1.44 (0.85–2.45)	0.170	1.18 (0.68–2.06)	0.550
Clinic	164 (71.6)	256 (34.2)	5.79 (3.74–8.96)	<0.001	2.64 (1.60–4.36)	<0.001

Others (University, research institution, government, health organization, etc.)	2 (0.87)	21 (2.8)	0.86 (0.19–3.86)	0.850	0.90 (0.22–3.73)	0.880
Providing daily paediatric medical service (≥ 10% of total patients)	113 (49.3)	170 (22.6)	3.33 (2.45–4.55)	<0.001	1.78 (1.24–2.55)	0.002
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	164 (71.6)	555 (74.0)	0.89 (0.64–1.23)	0.480	1.07 (0.73–1.55)	0.740
Experience of kindergarten or school physician	165 (72.1)	309 (41.1)	3.70 (2.68–5.11)	<0.001	2.12 (1.45–3.10)	<0.001
Experience raising children	176 (76.9)	545 (72.5)	1.26 (0.89–1.78)	0.190	0.86 (0.56–1.32)	0.480
Information resource						
Government	189 (82.5)	558 (74.2)	1.64 (1.13–2.40)	0.010	1.25 (0.82–1.90)	0.290
Academia	226 (98.7)	687 (91.4)	7.13 (2.22–22.90)	0.001	1.76 (0.55–5.64)	0.340
Commerce	71 (31.0)	212 (28.2)	1.14 (0.83–1.58)	0.410	0.85 (0.58–1.23)	0.380
Social network service or mailing list by individuals or group of medical service providers	94 (41.1)	205 (27.3)	1.86 (1.36–2.53)	<0.001	1.26 (0.88–1.80)	0.210
None	0	19 (2.5)	0.08 (0.05–1.36)*	0.081	0.35 (0.02–8.24)	0.520

*Penalized maximum likelihood logistic regression. PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

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TABLE 3 Factors associated with administration of HPV vaccine for voluntary vaccination

	PCPs who administer HPV vaccine, n=175 (17.8%)	PCPs who do not administer HPV vaccine, n=806 (82.2%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio* (95% CI), n=977	*p*-value
Factors	n (%)	n (%)	n (%)		n (%)	
High scores in vaccination quiz (4–6 points)	132 (75.4)	379 (47.0)	3.46 (2.39–5.01)	<0.001	2.71 (1.81–4.04)	<0.001
Sex: male	131 (74.8)	608 (75.4)	0.97 (0.66–1.41)	0.870	0.89 (0.59–1.35)	0.580
Postgraduate year (y)						
3–5	12 (6.9)	80 (9.9)	Reference		Reference	
6–10	21 (12.0)	157 (19.5)	0.89 (0.42–1.90)	0.770	0.48 (0.19–1.23)	0.130
11–20	66 (37.7)	292 (36.2)	1.51 (0.78–2.92)	0.230	0.69 (0.27–1.75)	0.430
21–30	41 (23.4)	152 (18.9)	1.80 (0.89–3.61)	0.099	0.97 (0.38–2.50)	0.960
31–40	28 (16.0)	106 (13.2)	1.76 (0.84–3.67)	0.130	0.98 (0.38–2.53)	0.970
≥41	7 (4.0)	19 (2.4)	2.46 (0.85–7.07)	0.096	1.35 (0.40–4.57)	0.630
Position of any specialist qualification	154 (88.0)	690 (85.7)	1.22 (0.74–2.01)	0.430	1.12 (0.59–2.12)	0.730
Main practice category: primary care	141 (80.6)	556 (69.0)	1.86 (1.25–2.79)	0.002	1.52 (0.93–2.49)	0.098
Practice setting						
University hospital or general hospital	36 (20.6)	245 (30.5)	Reference		Reference	
Other hospital	29 (16.6)	225 (28.0)	0.89 (0.52–1.48)	0.620	0.68 (0.39–1.19)	0.180
Clinic	109 (62.3)	311 (38.7)	2.39 (1.58–3.60)	<0.001	1.27 (0.77–2.08)	0.350

Others (University, research institution, government, health organization, etc.)	1 (0.57)	22 (2.7)	0.31 (0.04–2.37)	0.260	0.37 (0.06–2.10)	0.260
Providing daily paediatric medical service (≥10% of total patients)	66 (37.7)	217 (26.9)	1.64 (1.17–2.32)	0.005	1.04 (0.70–1.55)	0.840
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	135 (77.1)	584 (72.6)	1.27 (0.86–1.87)	0.220	1.26 (0.83–1.91)	0.270
Experience of kindergarten or school physician	106 (60.6)	368 (45.7)	1.83 (1.31–2.55)	<0.001	1.23 (0.82–1.84)	0.310
Experience raising children	129 (73.7)	592 (73.5)	1.01 (0.70–1.47)	0.070	0.70 (0.45–1.08)	0.110
Information resource						
Government	152 (86.9)	595 (73.8)	2.34 (1.47–3.73)	<0.001	1.90 (1.17–3.08)	0.009
Academia	170 (97.1)	743 (92.2)	2.88 (1.14–7.28)	0.025	0.93 (0.35–2.43)	0.880
Commerce	55 (31.4)	228 (28.3)	1.16 (0.82–1.66)	0.410	0.84 (0.57–1.25)	0.390
Social network service or mailing list by individuals or group of medical service providers	80 (45.7)	219 (27.2)	2.26 (1.61–3.16)	<0.001	1.82 (1.25–2.64)	0.002
None	0	19 (2.4)	0.12 (0.01–1.91)*	0.130	0.39 (0.02–8.00)	0.540

*Penalized maximum likelihood logistic regression. PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

TABLE 4 Factors associated with recommendation of HPV vaccine for routine vaccination

	PCPs who recommend HPV vaccine, n=408 (41.6%)	PCPs who do not recommend HPV vaccine, n=573 (58.4%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio (95% CI), n=977	*p*-value
Factors	n (%)	n (%)	n (%)		n (%)	
High scores in vaccination quiz (4–6 points)	248 (60.8)	263 (45.9)	1.83 (1.41–2.36)	<0.001	2.17 (1.62–2.92)	<0.001
Sex: male	319 (78.2)	420 (73.3)	1.31 (0.97–1.76)	0.080	1.37 (0.99–1.90)	0.056
Postgraduate year (y)						
3–5	44 (10.8)	48 (8.4)	Reference		Reference	
6–10	69 (16.9)	109 (19.0)	0.69 (0.42–1.15)	0.150	0.89 (0.47–1.68)	0.720
11–20	153 (37.5)	205 (35.8)	0.81 (0.51–1.29)	0.380	1.03 (0.53–1.99)	0.940
21–30	90 (22.1)	103 (18.0)	0.95 (0.58–1.57)	0.850	1.28 (0.64–2.53)	0.480
31–40	45 (11.0)	89 (15.5)	0.55 (0.32–0.95)	0.032	0.73 (0.36–1.48)	0.380
≥41	7 (1.7)	19 (3.3)	0.40 (0.15–1.05)	0.062	0.56 (0.19–1.62)	0.280
Position of any specialist qualification	347 (85.1)	497 (86.9)	0.86 (0.60–1.24)	0.410	0.79 (0.49–1.29)	0.350
Main practice category: primary care	281 (68.9)	416 (72.6)	0.84 (0.63–1.10)	0.210	0.79 (0.55–1.11)	0.180
Practice setting						
University hospital or general hospital	143 (33.8)	143 (25.1)	Reference		Reference	
Other hospital	101 (24.8)	219 (29.2)	0.68 (0.49–0.96)	0.030	0.69 (0.48–1.00)	0.048
Clinic	161 (39.5)	259 (45.4)	0.64 (0.47–0.87)	0.005	0.67 (0.46–0.98)	0.041

Others (University, research institution, government, health organization, etc.)	8 (2.0)	15 (2.6)	0.55 (0.23–1.34)	0.190	0.51 (0.20–1.31)	0.160
Providing daily paediatric medical service (≥10% of total patients)	95 (23.3)	188 (32.8)	0.62 (0.47–0.83)	0.001	0.50 (0.36–0.70)	<0.001
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	305 (74.9)	414 (72.4)	1.14 (0.85–1.52)	0.370	1.08 (0.78–1.47)	0.650
Experience of kindergarten or school physician	190 (46.6)	284 (49.6)	0.89 (0.69–1.14)	0.360	1.09 (0.80–1.49)	0.570
Experience raising children	296 (72.6)	425 (74.2)	0.92 (0.69–1.23)	0.570	0.79 (0.56–1.10)	0.160
Information resource						
Government	294 (72.1)	453 (79.1)	0.68 (0.51–0.92)	0.011	0.69 (0.50–0.96)	0.026
Academia	385 (94.4)	528 (92.2)	1.43 (0.85–2.40)	0.180	1.21 (0.63–2.35)	0.560
Commerce	113 (27.7)	170 (29.7)	0.91 (0.69–1.20)	0.500	0.91 (0.67–1.25)	0.560
Social network service or mailing list by individuals or group of medical service providers	136 (33.3)	163 (28.5)	1.26 (0.96–1.65)	0.100	1.33 (0.98–1.82)	0.071
None	7 (1.7)	12 (2.1)	0.82 (0.32–2.09)	0.670	0.82 (0.25–2.68)	0.740

1 PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

TABLE 5 Factors associated with recommendation of HPV vaccine for voluntary vaccination

	PCPs who recommend HPV vaccine, n=216 (22.0%)	PCPs who do not recommend HPV vaccine, n=765 (78.0%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio (95% CI), n=977	*p*-value
Factors	n (%)	n (%)	n (%)		n (%)	
High scores in vaccination quiz (4–6 points)	131 (60.6)	380 (49.7)	1.56 (1.15–2.12)	0.005	1.88 (1.32–2.67)	<0.001
Sex: male	174 (80.6)	565 (73.9)	1.47 (1.01–2.13)	0.045	1.67 (1.12–2.49)	0.012
Postgraduate year (y)						
3–5	24 (11.1)	68 (8.9)	Reference		Reference	
6–10	30 (13.9)	148 (19.4)	0.57 (0.31–1.06)	0.074	0.81 (0.37–1.75)	0.590
11–20	87 (40.3)	271 (35.4)	0.91 (0.54–1.54)	0.720	1.40 (0.63–3.08)	0.410
21–30	52 (24.1)	141 (18.4)	1.04 (0.59–1.84)	0.880	1.73 (0.77–3.88)	0.190
31–40	21 (9.7)	113 (14.8)	0.53 (0.27–1.02)	0.056	0.84 (0.36–1.98)	0.690
≥41	2 (0.9)	24 (3.1)	0.24 (0.05–1.02)	0.062	0.38 (0.07–1.89)	0.240
Position of any specialist qualification	184 (85.2)	660 (86.4)	0.91 (0.59–1.39)	0.65	0.74 (0.40–1.35)	0.320
Main practice category: primary care	148 (68.5)	549 (71.7)	0.86 (0.62–1.19)	0.35	0.84 (0.55–1.27)	0.400
Practice setting						
University hospital or general hospital	81 (37.5)	200 (26.3)	Reference		Reference	
Other hospital	53 (24.5)	201 (26.4)	0.65 (0.44–0.97)	0.030	0.69 (0.45–1.06)	0.091

Clinic	77 (35.7)	343 (45.0)	0.55 (0.39–0.79)	0.001	0.67 (0.43–1.04)	0.075
Others (University, research institution, government, health organization, etc.)	5 (2.3)	18 (2.4)	0.69 (0.25–1.91)	0.470	0.63 (0.21–1.84)	0.400
Providing daily paediatric medical service (≥10% of total patients)	43 (19.9)	240 (31.4)	0.54 (0.38–0.78)	0.001	0.52 (0.34–0.78)	0.002
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	171 (80.0)	547 (71.6)	1.59 (1.10–2.30)	0.014	1.42 (0.95–2.11)	0.084
Experience of kindergarten or school physician	87 (40.3)	387 (50.6)	0.66 (0.48–0.90)	0.008	0.79 (0.55–1.14)	0.210
Experience raising children	153 (70.8)	568 (74.3)	0.84 (0.60–1.18)	0.32	0.67 (0.45–1.00)	0.049
Information resource						
Government	155 (71.8)	592 (77.4)	0.74 (0.53–1.04)	0.087	0.80 (0.55–1.16)	0.240
Academia	202 (93.5)	711 (92.9)	1.10 (0.60–2.01)	0.770	0.94 (0.44–2.04)	0.880
Commerce	60 (27.8)	223 (29.2)	0.93 (0.67–1.31)	0.690	0.91 (0.63–1.32)	0.620
Social network service or mailing list by individuals or group of medical service providers	79 (36.6)	220 (28.8)	1.43 (1.04–1.96)	0.028	1.56 (1.09–2.24)	0.016
None	4 (1.9)	15 (2.0)	0.94 (0.31–2.87)	0.920	0.84 (0.21–3.40)	0.810

1 PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Figure Legends

Figure 1. Study flowchart

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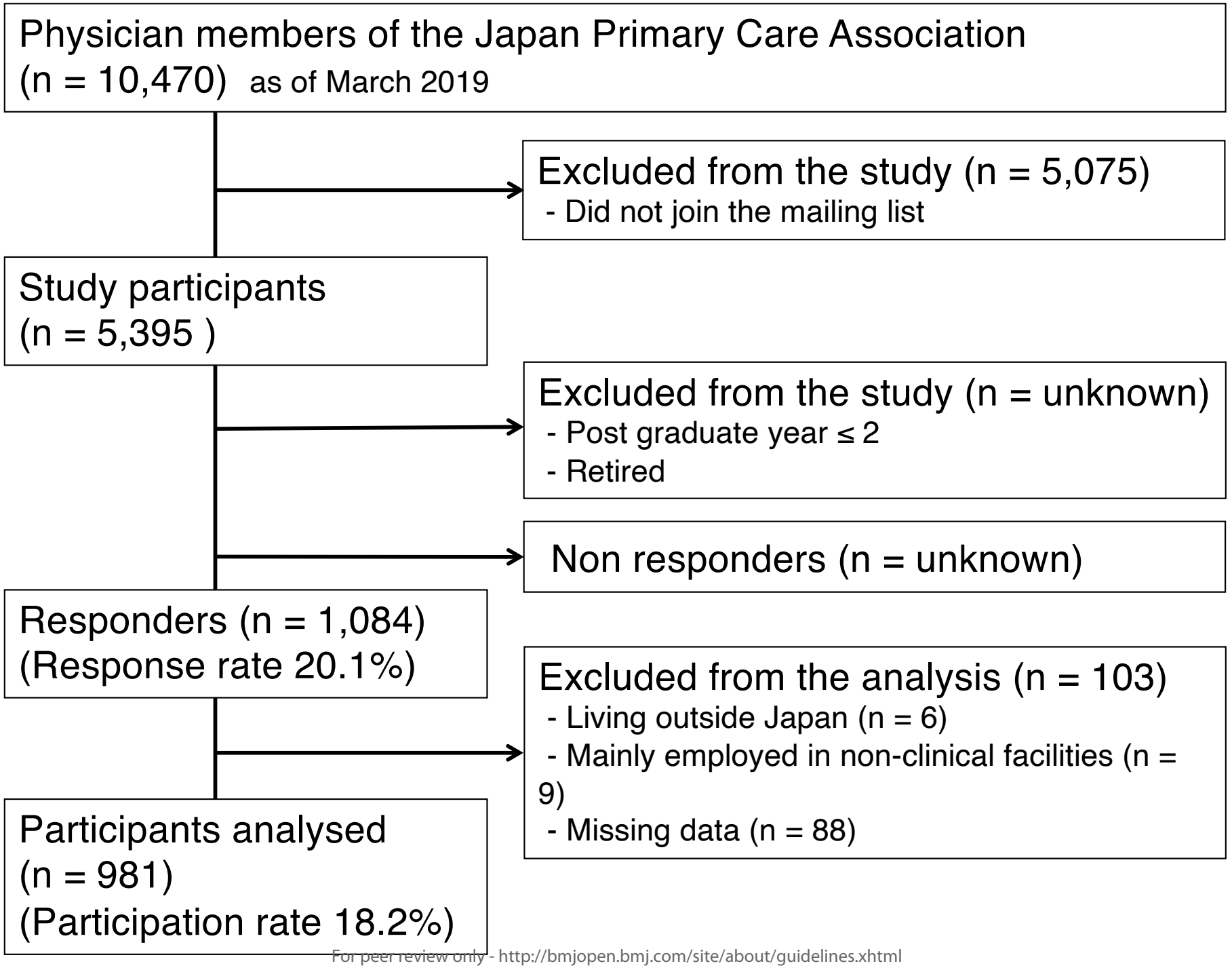
Physician members of the Japan Primary Care Association
(n = 10,470) as of March 2019
Excluded from the study (n = 5,075)
- Did not join the mailing list
Study participants
(n = 5,395)
Excluded from the study (n = unknown)
- Post graduate year ≤ 2
- Retired
Non responders (n = unknown)
Responders (n = 1,084)
(Response rate 20.1%)
Excluded from the analysis (n = 103)
- Living outside Japan (n = 6)
- Mainly employed in non-clinical facilities (n = 9)
- Missing data (n = 88)
Participants analysed
(n = 981)
(Participation rate 18.2%)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10,29
		(b) Give reasons for non-participation at each stage	10, 29
		(c) Consider use of a flow diagram	29
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	20
Outcome data	15*	Report numbers of outcome events or summary measures	11-12, 22-28
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12, 22-28
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan

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Primary Subject Heading:	General practice / Family practice
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TITLE PAGE

Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan

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ABSTRACT

Objective The Japanese government suspended the proactive recommendation of the human papillomavirus vaccine (HPVv) in 2013, and the vaccination rate of HPVv declined to <1% during 2014–2015. Previous studies have shown that the recommendation by a physician affects a recipient's decision to receive a vaccine, and physicians' accurate knowledge about vaccination is important to increase vaccine administration. This study aimed to evaluate the association between physicians' knowledge of vaccination and the administration or recommendation of HPVv by primary care physicians (PCPs) in the absence of proactive recommendations from the Japanese government.

Design Cross-sectional study analysed data obtained through a web-based, self-administered questionnaire survey.

Setting The questionnaire was distributed to Japan Primary Care Association (JPCA) members.

Participants JPCA members who were physicians and on the official JPCA mailing list (n=5,395) were included.

Primary and secondary outcome measures The primary and secondary outcomes were the administration and recommendation of HPVv, respectively, by PCPs. The association between PCPs' knowledge regarding vaccination and each outcome was determined based on their background and

vaccination quiz scores and a logistic regression analysis to estimate the adjusted odds ratios (AORs).

Results We received responses from 1,084 PCPs and included 981 of them in the analysis. PCPs with a higher score on the vaccination quiz were significantly more likely to administer the HPVv for routine and voluntary vaccination (AOR 2.28, 95% confidence interval [CI] 1.58–3.28; AOR 2.71, 95% CI 1.81–4.04, respectively) and recommend the HPVv for routine and voluntary vaccination than PCPs with a lower score (AOR 2.17, 95% CI 1.62–2.92; AOR 1.88, 95% CI 1.32–2.67, respectively).

Conclusions These results suggest that providing accurate knowledge regarding vaccination to PCPs may improve their administration and recommendation of HPVv, even in the absence of active government recommendations.

Strengths and limitations of this study

- This is the first study to evaluate the association between primary care physicians' (PCPs) vaccination knowledge and HPV vaccine administration and recommendation without proactive recommendation from the Japanese government.
- This nationwide study targeted the physician members of the Japan Primary Care Association, which is the largest academic society for PCPs in Japan.
- A limitation of this study was its potential selection bias due to the voluntary participation of the

PCPs in the survey.

- Furthermore, the effects of vaccine hesitancy among parents and media on the PCPs were not evaluated.

Data availability statement

Data are available from the corresponding author upon reasonable request.

Keywords: HPV vaccine; primary care physicians; administration; recommendation; vaccination

INTRODUCTION

The World Health Organization (WHO) recognises cervical cancer and other human papillomavirus (HPV)-related diseases as important global public health concerns and recommends the inclusion of HPV vaccines (HPVv) in national immunisation programmes.(1) In Japan, HPVv was introduced in 2009 as a voluntary vaccine without recommendation or funding from the government.(2, 3) In 2010, the Ministry of Health, Labour and Welfare (MHLW) initiated an urgent promotional campaign for vaccination, and the Government of Japan provided subsidies to local governments for HPVv.(2, 3) This campaign was successful, and the vaccination rate of HPVv increased to 70–80% in the targeted group of young girls in 2012.(3-6) In April 2013, free-of-charge HPV vaccination of 12- to 16-year-old girls was initiated as part of the routine vaccination programme.(3, 7, 8) On the other hand, three doses of voluntary bivalent HPVv for ≥10-year-old females and quadrivalent HPVv for ≥9-year-old females cost approximately ¥45,000 (US $450, as of April 2013). However, the media widely reported concerns regarding potential adverse effects of HPV vaccination among young girls, including complex regional pain syndrome, giving rise to social distrust and vaccine hesitancy related to HPVv.(3, 4, 7, 9) Consequently, the MHLW suspended proactive recommendation of HPV vaccination in June 2013;(7, 10) the local governments stopped sending individual notifications to the homes of girls eligible for HPVv although it continued being a part of the routine vaccine programme.(10) The HPV vaccination rate declined to less than 1% during 2014–2015.(5, 6)

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data of HPVv from 2008 to 2015 and found it to be extremely safe(11). In 2017, the GACVS expressed concerns regarding the situation in Japan, stating that the mortality rate from cervical cancer was expected to increase because HPVv was not proactively recommended.(11) In 2018, Suzuki et al. reported that there was no association between HPVv and adverse post-vaccination symptoms in Nagoya, Japan.(12) However, the MHLW did not resume the proactive recommendation of HPV vaccination as of 2019. Vaccine hesitancy has also been reported in other countries, and the WHO identified it as one of 10 threats to global health in 2019.(13)

Previous studies have shown that vaccine recommendation by a physician affects the recipient's decision in receiving a vaccine.(14-19) Physicians' accurate knowledge regarding vaccination is important to increase vaccine administration or recommendation rates.(20-22) In Japan, the HPVv is administered not only by paediatricians, obstetricians, and gynaecologists (OBGYNs), but also by primary care physicians (PCPs).(23, 24) A 2012 nationwide survey on practices and attitudes towards vaccination among PCPs in Japan(23, 24) showed that the proportion of PCPs administering and actively recommending HPVv was 58.3% and 46.5%, respectively.(23) A significant association between PCPs' awareness of public subsidies for HPVv and recommendation of HPVv vaccination was reported.(24) As previously indicated, the government vaccination policy for the HPVv changed following the survey(23, 24), and it was expected that these proportions would also change. However, the current fraction of PCPs administering or recommending the HPVv and the association

between PCPs' knowledge about vaccination and their attitude towards HPVv in Japan remain unknown. Therefore, this study aimed to evaluate the association between PCPs' knowledge about vaccination and the administration or recommendation of HPVv without proactive recommendation by the government.

METHODS

Study design, setting, and population

This cross-sectional study analysed data obtained from a web-based, self-administered questionnaire conducted by the Preventive Medicine and Health Promotion Committee Vaccine Team of the Japan Primary Care Association (JPCA), which is the largest academic association for PCPs in Japan. Most JPCA physicians were internists working as PCPs at clinics or hospitals. The survey was conducted from March to June 2019, and the inclusion criteria were JPCA members who were physicians and on the official mailing list for JPCA members. PCPs who were junior residents within 2 years after graduation from medical school were excluded, as this group cannot administer outpatient vaccinations without the supervision of attending physicians. We excluded PCPs who lived outside Japan, were retired, employed in a non-clinical setting, or had missing data.

Patient and public involvement

There was no patient or public involvement in this study.

Questionnaire

The questionnaire items were obtained from previous questionnaires administered by the Preventive Medicine and Health Promotion Committee Vaccine Team of JPCA(23, 24) and were distributed using the online mailing list for JPCA members. The questionnaire was conducted using an online tool, SurveyMonkey. The questionnaire was self-conducted and anonymous. It collected data on the participating physicians' attitudes regarding vaccines, including HPVv (administration or recommendation), through a vaccination quiz; information resources on vaccinations; and baseline characteristics, such as sex, career after graduation, main practice category, practice setting, provision of daily paediatric medical service, population size of the main working area as an administrative unit of the local government, experience as a kindergarten or school physician, and experience raising children (details below).

Main outcome

The primary outcome of this study was the administration of HPVv for routine and voluntary vaccination. The PCPs were asked to respond with 'yes' or 'no' to the following question: 'Do you administer routine/voluntary human papillomavirus vaccine?' Then, we investigated the association between PCPs' knowledge of vaccination and vaccine administration after adjusting for potential confounders (described below).

The secondary outcome of this study was the recommendation of routine and voluntary HPV vaccination by PCPs. The respondents were asked, 'How do you recommend routine/voluntary vaccination for HPV?' The following response options were provided using a Likert-type scale: 'actively recommend', 'recommend occasionally', 'no opinion', 'do not actively recommend', and 'do not recommend'. The response 'actively recommend' was considered 'recommending behaviour', which is a more positive behaviour.(15) Furthermore, the responses 'recommend occasionally', 'no opinion', 'do not actively recommend', and 'do not recommend' were considered 'non-recommending behaviour'. Then, we investigated the association between PCPs' knowledge of vaccination and vaccine recommendation after adjusting for possible confounders (described below).

Main factor

The main factor was PCPs' knowledge of vaccination, which was assessed based on a vaccination quiz. The quiz was created by the Preventive Medicine and Health Promotion Committee Vaccine Team of the JPCA using the Delphi method.(25) The quiz comprised six general vaccine questions encompassing Japanese vaccination affairs, including a question on HPVv. Scores of 0–6 were assigned based on the number of correct answers to each of the six questions. To obtain a binary variable, we designated scores above the average as high and those below the average as low. The vaccination quiz score (high or low) was considered an independent variable.

Vaccination quiz

Q1. A 12-year-old boy has no history of mumps vaccination according to the Maternal and Child Health Handbook. His mother states that he had developed mumps in his childhood. She mentions that he had visited a clinic with bilateral parotid gland swelling, and the doctor had suspected mumps based on clinical examination without blood tests. Is it then correct to recommend a mumps vaccine to the boy? (Correct answer: correct)

Q2. A 3-month pregnant woman requests an influenza vaccine, and the only available influenza vaccine in the hospital contains thimerosal. Is this vaccine acceptable or contraindicated for this patient? (Correct answer: acceptable)

Q3. Is the 23-valent pneumococcal vaccine, an inactivated vaccine, less likely to cause swelling when injected intramuscularly than when injected subcutaneously? (Correct answer: Correct)

Q4. Is there a limit to the number of vaccines (including live vaccines) that can be concurrently administered? (Correct answer: there is no limit)

Q5. Is it correct that 'suspending proactive recommendation of HPV vaccination' means 'withholding local governments from sending individual pre-vaccination screening questionnaires for HPV vaccine and notices to each household and actively calling for HPV vaccination through various media rather than the suspension of routine vaccination'? (Correct answer: correct)

Q6. Is it correct that under the 'Adverse Event Following Immunization reporting system', physicians are obligated to report to the Pharmaceuticals and Medical Devices Agency (PMDA) when a vaccinated individual begins exhibiting certain symptoms? (Correct answer: correct)

Other factors

Other factors included the physician's sex, postgraduate years (3–5, 6–10, 11–20, 21–30, 31–40, and ≥41 years), any specialist qualifications, including those related to primary care, main practice category (primary care; family physician, general practitioner, hospitalist/general physician or others; paediatricians, OBGYNs, industrial physician, researcher, administrative staff, and others), practice setting (e.g., university hospital or general hospital, other hospital, clinic, others; university, research institution, government, and health organisation), proportion of paediatric patients (number of paediatric patients with respect to the total patient population) that was high (≥10%) or low (<10%), main working area as an administrative unit of the local government in an urban area (≥50,000 people), experience as a kindergarten or school physician, experience raising children as a parent, and information resources about vaccinations (government, academic, commercial,(26) online professional community such as website/Facebook group/Twitter/JPCA mailing list,(27) and none).

Statistical analysis

We performed univariate and multivariate logistic regression analysis to estimate the odds ratios, adjusted odds ratios (AORs), and 95% confidence intervals (CIs), using binary variables for the main outcome. We investigated the association between PCPs' knowledge of vaccination and HPVv administration or recommendation.

Multiple logistic regression analysis was performed by adjusting for the following possible confounding factors: physician's sex, postgraduate year, possession of any specialist qualifications, including primary care, main practice category, practice setting, a high or low proportion of paediatric patients, experience raising children as a parent, and information resources about vaccinations.

We conducted a sensitivity analysis to inspect each variation only for HPVv knowledge (correct or incorrect) rather than for the total quiz score. We used penalized maximum likelihood logistic regression for the analyses when any confounding factors were completely separated.(28)

The analysis participants were selected after excluding participants with missing data for the main outcome, main factor, and the above-mentioned possible confounders.

All statistical analyses used two-tailed tests of significance, with significance set at $p < 0.05$.

Analyses were performed using Stata/SE 14.2 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study flow and demographics

Of the 10,470 physician members of the JPCA, 5,075 who did not subscribe to JPCA mails and were, therefore, not on the mailing list were excluded. We received responses from 1,084 of 5,395 PCPs, with a response rate of 20.1%. The respondents were from all 47 prefectures of Japan. An additional 103 participants were excluded because they lived outside Japan, performed nonclinical

work, or had missing data. The analysis included 981 participants (Figure 1). The median (interquartile range) score for the vaccination quiz was 4 (range, 2–5) points. The minimum and maximum scores were 0 and 6 points, respectively, and the mean (standard deviation) score was 3.47 (1.68) points. To obtain a binary variable, scores of ≥4 were designated as high, and scores of ≤3 as low. Evaluation of the participant baseline characteristics revealed that 739 (75.3%) participants were men, 358 (36.5%) had worked for 11–20 years after graduation, 420 (42.8%) worked in clinics, 719 (73.3%) worked in the urban areas, and 283 (28.9%) worked in a clinical setting where the proportion of paediatric patients was ≥10% (Table 1).

Factors associated with HPVv administration under routine vaccination

We found that 229 PCPs (23.3%) administered HPVv under routine vaccination (Table2). PCPs with higher vaccination quiz scores were significantly more likely to administer HPVv as routine vaccination than those with lower scores (AOR 2.28, 95% CI 1.58–3.28, $p < 0.001$) (Supplementary Table 1). There was also a positive association between the administration of routine HPV vaccination and PCPs who worked at clinics (AOR 2.64, 95% CI 1.60–4.36, $p < 0.001$), those who had a higher proportion of paediatric patients (AOR 1.78, 95% CI 1.24–2.55, $p = 0.002$), and those who had experience as a kindergarten or school physician (AOR 2.12, 95% CI 1.45–3.10, $p < 0.001$) (Supplementary Table 1).

Factors associated with HPVv administration under voluntary vaccination

We found that 175 PCPs (17.8%) administered HPVv under voluntary vaccination. PCPs with higher scores on the vaccination quiz were significantly more likely to administer HPVv as voluntary vaccination than those with lower scores (AOR 2.71, 95% CI 1.81–4.04, $p < 0.001$) (Supplementary Table 1). There was also a positive association between administration of voluntary HPVv and PCPs who acquired information from governments (AOR 1.90, 95% CI 1.17–3.08, $p = 0.009$) and those who participated in a social network service or mailing list from an individual or group of medical service providers (AOR 1.82, 95% CI 1.25–2.64, $p = 0.002$) (Supplementary Table 1).

Factors associated with HPVv recommendation under routine vaccination

The PCPs selected the following options regarding the recommendation of HPVv under routine vaccination: 'actively recommend', 408 PCPs (41.6%); 'recommend occasionally', 319 PCPs (32.5%); 'no opinion', 181 PCPs (18.5%); 'do not actively recommend', 49 (5.0%); and 'do not recommend', 24 (2.5%) (Table 2). PCPs with higher scores on the vaccination quiz were significantly more likely to recommend HPVv under routine vaccination than those with lower scores (AOR 2.17, 95% CI 1.62–2.92; $p < 0.001$) (Supplementary Table 2). However, there was a negative association between recommending routine HPV vaccination and PCPs who worked at other hospitals (AOR 0.69, 95% CI 0.48–1.00, $p = 0.048$) and clinics (AOR 0.67, 95% CI 0.46–0.98, $p = 0.041$), those who had a higher proportion of paediatric patients (AOR 0.50, 95% CI 0.36–0.70, p

< 0.001), and those who acquired information from government sources (AOR 0.69, 95% CI 0.50–0.96, $p = 0.026$) (Supplementary Table 2).

Factors associated with HPVv recommendation under voluntary vaccination

The PCPs selected the following options regarding the recommendation of HPVv under voluntary vaccination: 'actively recommend', 216 PCPs (22.0%); 'recommend occasionally', 358 (36.5%); 'no opinion', 288 (29.4%); 'do not actively recommend', 75 (7.7%); and 'do not recommend', 44 (4.5%) (Table 2).

PCPs with higher vaccination quiz scores were significantly more likely to recommend HPVv under voluntary vaccination than those with low scores (AOR 1.88, 95% CI 1.32–2.67, $p < 0.001$) (Supplementary Table 2). There was also a positive association between the recommendation of voluntary HPV vaccination and PCPs who were male (AOR 1.67, 95% CI 1.12–2.49, $p = 0.012$) and those who participated in a social network service or mailing list for medical service from an individual or group of providers (AOR 1.56, 95% CI 1.09–2.24, $p = 0.016$). However, there was a negative association between the recommendation of voluntary HPV vaccination and PCPs who had a higher proportion of paediatric patients (AOR 0.52, 95% CI, 0.34–0.78, $p = 0.002$) and those who had experience raising children (AOR 0.67, 95% CI 0.45–1.00, $p = 0.049$) (Supplementary Table 2).

The correlation coefficient between vaccine administration and recommendation for routine and voluntary HPV vaccination was 0.17 and 0.23, respectively.

Sensitivity analysis

PCPs with correct responses to the HPV vaccination quiz were significantly more likely to administer HPVv than those with incorrect responses regarding routine vaccination (AOR 2.06, 95% CI 1.38–3.09, $p < 0.001$) and voluntary vaccination (AOR 2.16, 95% CI 1.39–3.34, $p = 0.001$).

PCPs with correct responses to the HPV vaccination quiz were also significantly more likely to recommend HPV vaccination than those with incorrect responses regarding routine (AOR 1.51, 95% CI 1.12–2.04, $p = 0.006$) and voluntary vaccination (AOR 1.53, 95% CI 1.07–2.19, $p = 0.02$).

DISCUSSION

Vaccine hesitancy is a global health concern(13), and hesitancy for HPV vaccination has been reported in many countries, including Japan.(4-6) This is the first study to focus on the association between PCPs' knowledge of vaccination and their practice or attitude towards HPVv in the absence of proactive recommendations from the government of Japan. We found positive associations between accurate vaccination knowledge among PCPs and the administration or recommendation of HPVv under routine and voluntary vaccination. In addition, the sensitivity analysis showed that physicians with accurate knowledge of HPV vaccination were likely to recommend HPVv.

A 2021 systematic review of 96 papers from 34 countries examined the perceptions, knowledge, and recommendations of healthcare providers regarding vaccines. It showed that the healthcare providers' recommendations were positively associated with their knowledge and experience, beliefs about disease risk, and perceptions of vaccine safety, necessity, and efficacy.(29) The present results are consistent with these findings.(29) In Lebanon, where HPVv is not included in the national routine vaccination schedule as of 2017, physicians practicing in obstetrics and gynaecology, paediatrics, family medicine, and infectious diseases with greater knowledge regarding HPV and HPVv recommend HPVv more often than physicians with less knowledge (AOR 3.4).(30) Further, in the United States, higher rates of completion of three HPVv doses (IRR 1.28) were observed among the patients of primary care clinicians, including family medicine physicians, paediatricians, and family and paediatric nurse-practitioners, with greater knowledge regarding HPV and HPVv (31). Our results also support these findings. Another study investigating the association between PCPs' knowledge of vaccination and the administration or recommendation of voluntary mumps vaccination for adults showed the same positive associations.(32)

Compared to that in our previous study from 2012,(23) the proportion of PCPs recommending or administering HPVv was lower in the present study: the proportion of HPVv administration decreased from 58.3%(23) to 23.3% for routine vaccination (Table 2). The proportion of PCPs recommending HPVv decreased from 46.5%(23) to 41.6% for routine vaccination (Table 2).

A study conducted among paediatricians in Osaka, Japan, in 2020 and 2021 revealed that the proportion of paediatricians who administered or actively recommended the HPVv for routine vaccination was 44.5% and 32.5% in 2020 and 67.9% and 40% in 2021, respectively.(33) In addition, a study conducted among OBGYNs in Osaka, Japan, showed that the proportion of OBGYNs recommending the HPVv for teenagers was 70.1% in 2017(3) and 84.6% in 2019.(34) As of 2018, the proportion of family physicians and paediatricians in the United States administering the HPVv was 84.1% and 95.3%, respectively,(35) and the proportion of those who strongly recommended the HPVv was 72–90% and 85–99% (11- to 12-year-old, 13- to 14-year-old, and ≥15-year-old female patients), respectively.(35) Our study revealed that in Japan, PCPs may administer routine HPVv less than paediatricians(33) and actively recommend routine HPVv more than paediatricians(33) but less than OBGYNs.(3) In addition, our study shows that Japanese PCPs may administer or recommend the HPVv less than family physicians in the United States.(35)

We also found positive associations between different information resources and administration or recommendation of voluntary HPV vaccination. Information resources from social network services or mailing lists from medical service providers seem to be positively associated with the administration or recommendation of voluntary HPV vaccination. This might be because PCPs use virtual communities as valuable knowledge portals for clinically relevant information(36) and could be interested in how and why other physicians recommend and administer vaccination.(22, 32) Government information resources were positively associated with the administration of voluntary

HPVv but were negatively associated with the recommendation of routine HPVv. As of 2019, the MHLW had not resumed the proactive recommendation of routine HPV vaccination. Although the suspension of proactive recommendation was not intended to discontinue routine vaccination, it may have been misinterpreted as discontinuation of routine vaccination by some PCPs. Therefore, PCPs referring to government sources for information regarding this policy may administer HPVv as part of voluntary instead of routine vaccination and may not recommend routine HPV vaccination. Alternatively, PCPs aware of the suspension may lose confidence to recommend the HPVv. A previous study reported that the lack of government recommendations was a barrier for PCPs to recommend vaccination.(23) In November 2021, the MHLW ended this suspension and resumed proactively recommending HPV vaccination for girls born in or after the fiscal year (FY) 2006, beginning in April 2022(37), and provided 'catch-up vaccinations' for 3 years, from April 2022 to March 2025, for females born from FY1997 to FY2005, who became eligible for routine HPV vaccination and may have missed the opportunity to receive the vaccination because of the suspension.(38, 39) The results of our study suggest that providing accurate knowledge and information about HPV vaccination to PCPs may help promote HPVv administration and recommendation by PCPs and thereby increase the vaccination rate. The JPCA vaccine team provides information about vaccination through websites(40) and regular onsite and online vaccine seminars for physicians.(41) Further research can help determine the optimal methods to provide accurate knowledge regarding vaccination to health care providers with vaccine hesitancy.(42)

Our study also shows that PCPs working at clinics, providing daily paediatric medical services (more than 10% of total patients), and with experience as kindergarten or school physicians tend to administer routine HPV vaccination (Supplementary Table 1). The target population for routine HPV vaccination is 12- to 16-year-old girls, and PCPs experienced in treating this group may better understand the need for routine vaccination; therefore, they may be more likely to administer the vaccine. In contrast, PCPs working at clinics or other hospitals providing daily paediatric medical services (more than 10% of total patients) were less likely to recommend routine HPV vaccination (Supplementary Table 2). In addition, PCPs providing daily paediatric medical services (more than 10% of total patients) and with experience in raising children tended to be less likely to recommend voluntary HPV vaccination (Supplementary Table 2). These results suggest that PCPs with more opportunity to provide medical service to 12- to 16-year-old girls may have less confidence to recommend the HPVv during the suspension of proactive recommendation by the MHLW or may be more affected by the anxiousness or hesitancy of the parents.(19, 23, 43)

This study has some limitations. First, there was a potential selection bias due to the low response rate. PCPs who more actively promoted vaccination may have been more likely to respond, and the actual proportion of PCPs administering or recommending HPVv may be lower. Second, our study did not consider voluntary HPV vaccination for men. In Japan, as of 2019, the target group for both routine and voluntary HPV vaccination included only women. However, in 2020, administration of voluntary quadrivalent HPVv was approved for men. Third, our study did not evaluate 9-valent

HPVv for voluntary vaccination, although in 2021, the 9-valent HPVv was approved for voluntary vaccination(44) and will be approved for routine vaccination from April 2023 onwards.(45) Future studies should include both men and women and consider the 9-valent HPVv. Fourth, we did not evaluate the effects of vaccine hesitancy among parents or mainstream media and social media on the PCPs.(43) The effect of vaccine hesitancy should be considered as one of the exposures in future studies. Fifth, we did not evaluate the effects of unknown confounding factors, which is a general limitation of observational studies. Finally, although the study participants were physician members of the JPCA, the largest society for PCPs in Japan, the generalisability of the results to PCPs outside of Japan is unclear. The policy for HPVv administration in Japan(38) changed after this study was conducted, and further surveys are needed to assess the current situation of HPVv administration and attitudes among PCPs.

Our results suggest that providing accurate knowledge regarding vaccination to PCPs may improve their administration and recommendation of the HPVv, even in the absence of active government recommendations.

CONCLUSIONS

We revealed a positive association between PCPs' knowledge of vaccines and the administration or recommendation of routine and voluntary HPV vaccination without a proactive recommendation from the government. Several factors influence PCPs' perception of HPV vaccinations, ultimately

affecting public healthcare. The results of our study can be applied to other countries with similar vaccination-related concerns, such as vaccine hesitancy and disagreements on vaccine policy between the scientific community and governments.(9, 46)

Our results suggest that providing more knowledge about vaccination to PCPs may increase their likelihood to administer or recommend the HPVv, thereby improving vaccination rates.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

We obtained written informed consent from all participants before conducting the survey.

Ethics approval

The study protocol was approved by the Institutional Review Board of Osaka Medical College (Rin-763).

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TABLES

TABLE 1 Characteristics of the participants

	Participants, n=981
	n (%)
Sex: male	739 (75.3), Missing 0
Postgraduate year (y)	Missing 0
3–5	92 (9.4)
6–10	178 (18.1)
11–20	358 (36.5)
21–30	193 (19.7)
31–40	134 (13.7)
≥41	26 (2.7)
Main practice category: primary care	697 (71.1), Missing 0
Practice setting	Missing 3 (0.3)
University hospital or general hospital	281 (28.6)
Other hospital	254 (25.9)
Clinic	420 (42.8)
Others (e.g., University, research institution, government, and health organisation)	23 (2.3)
Providing daily paediatric medical service (≥ 10% of total patients)	283 (28.9), Missing 0
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	719 (73.3), Missing 2 (0.2)
Experience as kindergarten or school physician	474 (48.3), Missing 0
Experience raising children	721 (73.5), Missing 0

Main practice category: primary care: Answered main practice category as family physician or general practitioner or hospitalist/general physician

TABLE 2 Vaccination quiz scores and HPV vaccine administration or recommendation levels among primary care physicians

Vaccination quiz	Total, n (%)	Administration of HPV vaccine	Recommendation level for HPV vaccine, n (%)				
			Actively recommend	Recommend occasionally	No opinion	Do not actively recommend	Do not recommend
		Routine HPV vaccination, n=981					
		Voluntary HPV vaccination, n=981					
High scores (4–6 points)	511 (52.1)	172 (33.7)	248 (48.5)	179 (35.0)	59 (11.6)	19 (3.7)	6 (1.2)
		132 (25.8)	131 (25.6)	211 (41.3)	120 (23.5)	31 (6.1)	18 (3.5)
Low scores (0–3 points)	470 (47.9)	57 (12.1)	160 (34.0)	140 (29.8)	122 (26.0)	30 (6.4)	18 (3.8)
		43 (9.2)	85 (18.1)	147 (31.3)	168 (35.7)	44 (9.4)	26 (5.5)
Total	981 (100)	229 (23.3)	408 (41.6)	319 (32.5)	181 (18.5)	49 (5.0)	24 (2.5)
		175 (17.8)	216 (22.0)	358 (36.5)	288 (29.4)	75 (7.7)	44 (4.5)

HPV, human papillomavirus

Figure Legends

Figure 1. Study flowchart

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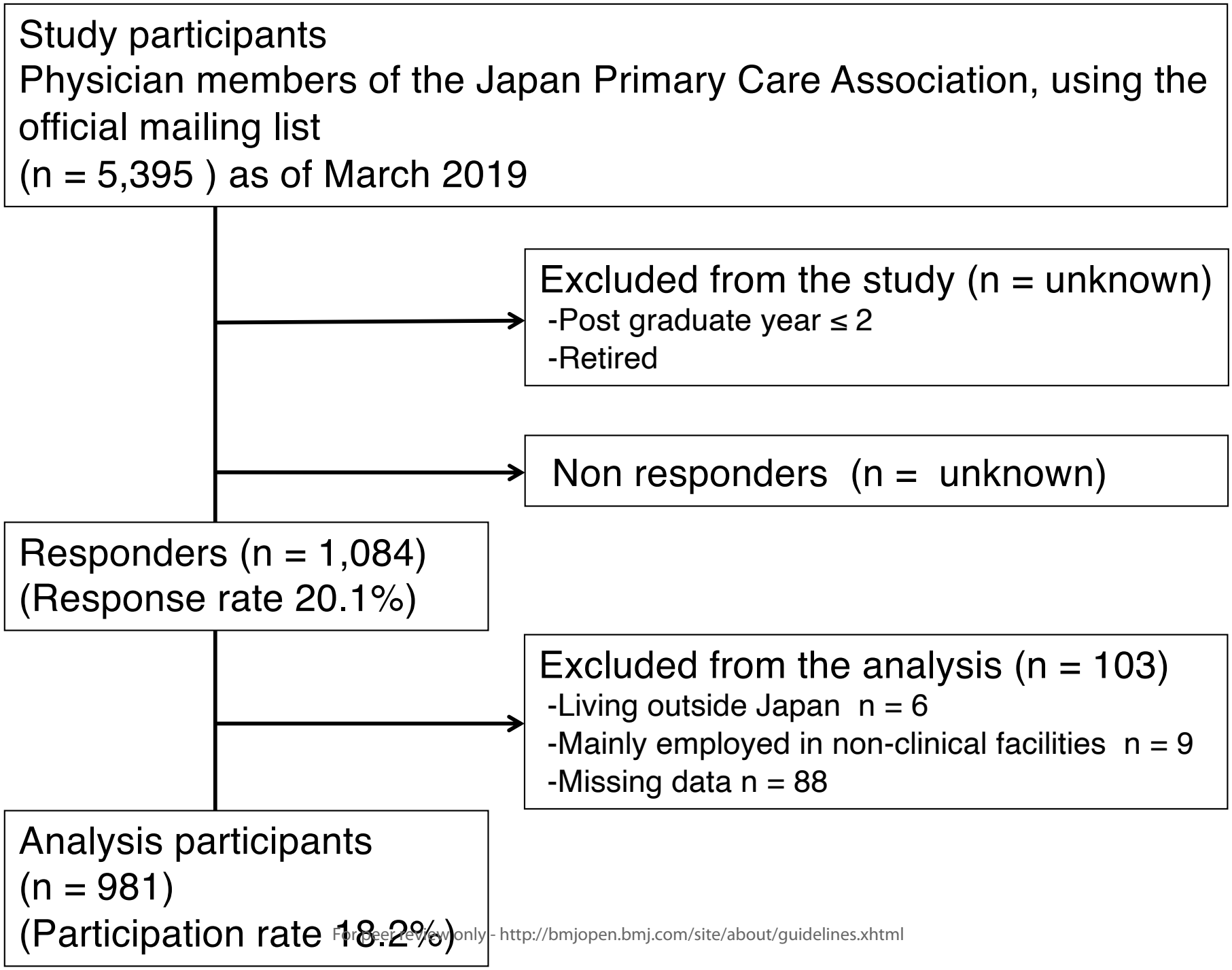

Supplementary Table 1 Factors associated with administration of HPV vaccine for routine and voluntary vaccination

	PCPs who administer HPV vaccine	PCPs who do not administer HPV vaccine	Crude odds ratio (95% CI)		Adjusted odds ratio* (95% CI)	
	Routine vaccination, n=229 (23.3%)	Routine vaccination, n=752 (76.7%)	Routine vaccination, n=981	*p* -value	Routine vaccination, n=977	*p* -value
	Voluntary vaccination, n=175 (17.8%)	Voluntary vaccination, n=806 (82.2%)	Voluntary vaccination, n=981		Voluntary vaccination, n=977	
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	172 (75.1)	339 (45.1)	3.68 (2.64–5.12)	<0.001	2.28 (1.58–3.28)	<0.001
	132 (75.4)	379 (47.0)	3.46 (2.39–5.01)	<0.001	2.71 (1.81–4.04)	<0.001
Sex: male	178 (77.7)	561 (74.6)	1.19 (0.84–1.69)	0.38	1.11 (0.75–1.65)	0.6
	131 (74.8)	608 (75.4)	0.97 (0.66–1.41)	0.87	0.89 (0.59–1.35)	0.58
Postgraduate year (y)						
3-5	14 (6.1)	78 (10.4)	Reference		Reference	
	12 (6.9)	80 (9.9)	Reference		Reference	
6-10	28 (12.2)	150 (20.0)	1.04 (0.52–2.09)	0.91	0.48 (0.20–1.18)	0.11
	21 (12.0)	157 (19.5)	0.89 (0.42–1.90)	0.77	0.48 (0.19–1.23)	0.13
11-20	95 (41.5)	263 (35.0)	2.01 (1.09–3.72)	0.026	0.83 (0.34–2.02)	0.68
	66 (37.7)	292 (36.2)	1.51 (0.78–2.92)	0.23	0.69 (0.27–1.75)	0.43
21–30	51 (22.3)	142 (18.9)	2.00 (1.04–3.84)	0.037	0.91 (0.37–2.27)	0.85
	41 (23.4)	152 (18.9)	1.80 (0.89–3.61)	0.099	0.97 (0.38–2.50)	0.96
31–40	34 (14.9)	100 (13.3)	1.89 (0.95–3.77)	0.069	0.80 (0.32–1.99)	0.63
	28 (16.0)	106 (13.2)	1.76 (0.84–3.67)	0.13	0.98 (0.38–2.53)	0.97
≥41	7 (3.1)	19 (2.5)	2.05 (0.73–5.79)	0.17	0.79 (0.23–2.67)	0.7
	7 (4.0)	19 (2.4)	2.46 (0.85–7.07)	0.096	1.35 (0.40–4.57)	0.63
Position of any specialist qualification	201 (87.8)	643 (85.6)	1.21 (0.77–1.88)	0.41	1.04 (0.57–1.89)	0.89
	154 (88.0)	690 (85.7)	1.22 (0.74–2.01)	0.43	1.12 (0.59–2.12)	0.73
Main practice category: primary care	183 (79.9)	514 (68.4)	1.84 (1.29–2.63)	0.001	1.18 (0.74–1.88)	0.5
	141 (80.6)	556 (69.0)	1.86 (1.25–2.79)	0.002	1.52 (0.93–2.49)	0.098
Practice setting						
University hospital or general hospital	28 (12.2)	253 (33.8)	Reference		Reference	
	36 (20.6)	245 (30.5)	Reference		Reference	
Other hospital	35 (15.3)	219 (29.2)	1.44 (0.85–2.45)	0.17	1.18 (0.68–2.06)	0.55
	29 (16.6)	225 (28.0)	0.89 (0.52–1.48)	0.62	0.68 (0.39–1.19)	0.18
Clinic	164 (71.6)	256 (34.2)	5.79 (3.74–8.96)	<0.001	2.64 (1.60–4.36)	<0.001
	109 (62.3)	311 (38.7)	2.39 (1.58–3.60)	<0.001	1.27 (0.77–2.08)	0.35
Others (i.e., University, research institution, government, and health organisation)	2 (0.87)	21 (2.8)	0.86 (0.19–3.86)	0.85	0.90 (0.22–3.73)	0.88
	1 (0.57)	22 (2.7)	0.31 (0.04–2.37)	0.26	0.37 (0.06–2.10)	0.26
Providing daily paediatric medical service (≥ 10% of total patients)	113 (49.3)	170 (22.6)	3.33 (2.45–4.55)	<0.001	1.78 (1.24–2.55)	0.002
	66 (37.7)	217 (26.9)	1.64 (1.17–2.32)	0.005	1.04 (0.70–1.55)	0.84
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	164 (71.6)	555 (74.0)	0.89 (0.64–1.23)	0.48	1.07 (0.73–1.55)	0.74
	135 (77.1)	584 (72.6)	1.27 (0.86–1.87)	0.22	1.26 (0.83–1.91)	0.27
Experience as kindergarten or school physician	165 (72.1)	309 (41.1)	3.70 (2.68–5.11)	<0.001	2.12 (1.45–3.10)	<0.001
	106 (60.6)	368 (45.7)	1.83 (1.31–2.55)	<0.001	1.23 (0.82–1.84)	0.31
Experience raising children	176 (76.9)	545 (72.5)	1.26 (0.89–1.78)	0.19	0.86 (0.56–1.32)	0.48
	129 (73.7)	592 (73.5)	1.01 (0.70–1.47)	0.07	0.70 (0.45–1.08)	0.11
Information resource						
Government	189 (82.5)	558 (74.2)	1.64 (1.13–2.40)	0.01	1.25 (0.82–1.90)	0.29
	152 (86.9)	595 (73.8)	2.34 (1.47–3.73)	<0.001	1.90 (1.17–3.08)	0.009
Academia	226 (98.7)	687 (91.4)	7.13 (2.22–22.90)	0.001	1.76 (0.55–5.64)	0.34
	170 (97.1)	743 (92.2)	2.88 (1.14–7.28)	0.025	0.93 (0.35–2.43)	0.88
Commerce	71 (31.0)	212 (28.2)	1.14 (0.83–1.58)	0.41	0.85 (0.58–1.23)	0.38
	55 (31.4)	228 (28.3)	1.16 (0.82–1.66)	0.41	0.84 (0.57–1.25)	0.39
Social network service or mailing list by individuals or group of medical service providers	94 (41.1)	205 (27.3)	1.86 (1.36–2.53)	<0.001	1.26 (0.88–1.80)	0.21
	80 (45.7)	219 (27.2)	2.26 (1.61–3.16)	<0.001	1.82 (1.25–2.64)	0.002
None	0	19 (2.5)	0.08 (0.05–1.36)*	0.081	0.35 (0.02–8.24)	0.52
	0	19 (2.4)	0.12 (0.01–1.91)*	0.13	0.39 (0.02–8.00)	0.54

*Penalized maximum likelihood logistic regression. PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Supplementary Table 2 Factors associated with recommendation of HPV vaccine for routine and voluntary vaccinatio

	PCPs who recommend HPV vaccine	PCPs who do not recommend HPV vaccine	Crude odds ratio (95% CI)		Adjusted odds ratio (95% CI)	
	Routine vaccination, n=408 (41.6%)	Routine vaccination, n=573 (58.4%)	Routine vaccination, n=981	*p* -value	Routine vaccination, n=977	*p* -value
	Voluntary vaccination, n=216 (22.0%)	Voluntary vaccination, n=765 (78.0%)	Voluntary vaccination, n=981		Voluntary vaccination, n=977	
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	248 (60.8)	263 (45.9)	1.83 (1.41–2.36)	<0.001	2.17 (1.62–2.92)	<0.001
	131 (60.6)	380 (49.7)	1.56 (1.15–2.12)	0.005	1.88 (1.32–2.67)	<0.001
Sex: male	319 (78.2)	420 (73.3)	1.31 (0.97–1.76)	0.08	1.37 (0.99–1.90)	0.056
	174 (80.6)	565 (73.9)	1.47 (1.01–2.13)	0.045	1.67 (1.12–2.49)	0.012
Postgraduate year (y)						
3-5	44 (10.8)	48 (8.4)	Reference		Reference	
	24 (11.1)	68 (8.9)	Reference		Reference	
6-10	69 (16.9)	109 (19.0)	0.69 (0.42–1.15)	0.15	0.89 (0.47–1.68)	0.72
	30 (13.9)	148 (19.4)	0.57 (0.31–1.06)	0.074	0.81 (0.37–1.75)	0.59
11-20	153 (37.5)	205 (35.8)	0.81 (0.51–1.29)	0.38	1.03 (0.53–1.99)	0.94
	87 (40.3)	271 (35.4)	0.91 (0.54–1.54)	0.72	1.40 (0.63–3.08)	0.41
21–30	90 (22.1)	103 (18.0)	0.95 (0.58–1.57)	0.85	1.28 (0.64–2.53)	0.48
	52 (24.1)	141 (18.4)	1.04 (0.59–1.84)	0.88	1.73 (0.77–3.88)	0.19
31–40	45 (11.0)	89 (15.5)	0.55 (0.32–0.95)	0.032	0.73 (0.36–1.48)	0.38
	21 (9.7)	113 (14.8)	0.53 (0.27–1.02)	0.056	0.84 (0.36–1.98)	0.69
≥41	7 (1.7)	19 (3.3)	0.40 (0.15–1.05)	0.062	0.56 (0.19–1.62)	0.28
	2 (0.9)	24 (3.1)	0.24 (0.05–1.02)	0.062	0.38 (0.07–1.89)	0.24
Position of any specialist qualification	347 (85.1)	497 (86.9)	0.86 (0.60–1.24)	0.41	0.79 (0.49–1.29)	0.35
	184 (85.2)	660 (86.4)	0.91 (0.59–1.39)	0.65	0.74 (0.40–1.35)	0.32
Main practice category: primary care	281 (68.9)	416 (72.6)	0.84 (0.63–1.10)	0.21	0.79 (0.55–1.11)	0.18
	148 (68.5)	549 (71.7)	0.86 (0.62–1.19)	0.35	0.84 (0.55–1.27)	0.4
Practice setting						
University hospital or general hospital	143 (33.8)	143 (25.1)	Reference		Reference	
	81 (37.5)	200 (26.3)	Reference		Reference	
Other hospital	101 (24.8)	219 (29.2)	0.68 (0.49–0.96)	0.03	0.69 (0.48–1.00)	0.048
	53 (24.5)	201 (26.4)	0.65 (0.44–0.97)	0.03	0.69 (0.45–1.06)	0.091
Clinic	161 (39.5)	259 (45.4)	0.64 (0.47–0.87)	0.005	0.67 (0.46–0.98)	0.041
	77 (35.7)	343 (45.0)	0.55 (0.39–0.79)	0.001	0.67 (0.43–1.04)	0.075
Others (e.g., University, research institution, government, and health organisation)	8 (2.0)	15 (2.6)	0.55 (0.23–1.34)	0.19	0.51 (0.20–1.31)	0.16
	5 (2.3)	18 (2.4)	0.69 (0.25–1.91)	0.47	0.63 (0.21–1.84)	0.4
Providing daily paediatric medical service (≥10% of total patients)	95 (23.3)	188 (32.8)	0.62 (0.47–0.83)	0.001	0.50 (0.36–0.70)	<0.001
	43 (19.9)	240 (31.4)	0.54 (0.38–0.78)	0.001	0.52 (0.34–0.78)	0.002
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	305 (74.9)	414 (72.4)	1.14 (0.85–1.52)	0.37	1.08 (0.78–1.47)	0.65
	171 (80.0)	547 (71.6)	1.59 (1.10–2.30)	0.014	1.42 (0.95–2.11)	0.084
Experience as kindergarten or school physician	190 (46.6)	284 (49.6)	0.89 (0.69–1.14)	0.36	1.09 (0.80–1.49)	0.57
	87 (40.3)	387 (50.6)	0.66 (0.48–0.90)	0.008	0.79 (0.55–1.14)	0.21
Experience raising children	296 (72.6)	425 (74.2)	0.92 (0.69–1.23)	0.57	0.79 (0.56–1.10)	0.16
	153 (70.8)	568 (74.3)	0.84 (0.60–1.18)	0.32	0.67 (0.45–1.00)	0.049
Information resource						
Government	294 (72.1)	453 (79.1)	0.68 (0.51–0.92)	0.011	0.69 (0.50–0.96)	0.026
	155 (71.8)	592 (77.4)	0.74 (0.53–1.04)	0.087	0.80 (0.55–1.16)	0.24
Academia	385 (94.4)	528 (92.2)	1.43 (0.85–2.40)	0.18	1.21 (0.63–2.35)	0.56
	202 (93.5)	711 (92.9)	1.10 (0.60–2.01)	0.77	0.94 (0.44–2.04)	0.88
Commerce	113 (27.7)	170 (29.7)	0.91 (0.69–1.20)	0.5	0.91 (0.67–1.25)	0.56
	60 (27.8)	223 (29.2)	0.93 (0.67–1.31)	0.69	0.91 (0.63–1.32)	0.62
Social network service or mailing list by individuals or group of medical service providers	136 (33.3)	163 (28.5)	1.26 (0.96–1.65)	0.1	1.33 (0.98–1.82)	0.071
	79 (36.6)	220 (28.8)	1.43 (1.04–1.96)	0.028	1.56 (1.09–2.24)	0.016
None	7 (1.7)	12 (2.1)	0.82 (0.32–2.09)	0.67	0.82 (0.25–2.68)	0.74
	4 (1.9)	15 (2.0)	0.94 (0.31–2.87)	0.92	0.84 (0.21–3.40)	0.81

PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Checklist for Reporting Of Survey Studies (CROSS)

Section/topic	Item	Item description	Reported on page #
Title and abstract			
Title and abstract	1a	State the word "survey" along with a commonly used term in title or abstract to introduce the study's design.	3
	1b	Provide an informative summary in the abstract, covering background, objectives, methods, findings/results, interpretation/discussion, and conclusions.	3-4
Introduction			
Background	2	Provide a background about the rationale of study, what has been previously done, and why this survey is needed.	6-8
Purpose/aim	3	Identify specific purposes, aims, goals, or objectives of the study.	8
Methods			
Study design	4	Specify the study design in the methods section with a commonly used term (e.g., cross-sectional or longitudinal).	8-9
Data collection methods	5a	Describe the questionnaire (e.g., number of sections, number of questions, number and names of instruments used).	9
	5b	Describe all questionnaire instruments that were used in the survey to measure particular concepts. Report target population, reported validity and reliability information, scoring/classification procedure, and reference links (if any).	9
	5c	Provide information on pretesting of the questionnaire, if performed (in the article or in an online supplement).	-

		Report the method of pretesting, number of times questionnaire was pre-tested, number and demographics of participants used for pretesting, and the level of similarity of demographics between pre-testing participants and sample population.	
	5d	Questionnaire if possible, should be fully provided (in the article, or as appendices or as an online supplement).	-
	6a	Describe the study population (i.e., background, locations, eligibility criteria for participant inclusion in survey, exclusion criteria).	8-9
Sample characteristics	6b	Describe the sampling techniques used (e.g., single stage or multistage sampling, simple random sampling, stratified sampling, cluster sampling, convenience sampling). Specify the locations of sample participants whenever clustered sampling was applied.	9
	6c	Provide information on sample size, along with details of sample size calculation.	-
	6d	Describe how representative the sample is of the study population (or target population if possible), particularly for population-based surveys.	-
Survey administration	7a	Provide information on modes of questionnaire administration, including the type and number of contacts, the location where the survey was conducted (e.g., outpatient room or by use of online tools, such as SurveyMonkey).	9
	7b	Provide information of survey's time frame, such as periods of recruitment, exposure, and follow-up days.	8
	7c	Provide information on the entry process: –>For non-web-based surveys, provide approaches to	-

		minimize human error in data entry. –>For web-based surveys, provide approaches to prevent "multiple participation" of participants.	
Study preparation	8	Describe any preparation process before conducting the survey (e.g., interviewers' training process, advertising the survey).	-
Ethical considerations	9a	Provide information on ethical approval for the survey if obtained, including informed consent, institutional review board [IRB] approval, Helsinki declaration, and good clinical practice [GCP] declaration (as appropriate).	23
	9b	Provide information about survey anonymity and confidentiality and describe what mechanisms were used to protect unauthorized access.	9
Statistical analysis	10a	Describe statistical methods and analytical approach. Report the statistical software that was used for data analysis.	13
	10b	Report any modification of variables used in the analysis, along with reference (if available).	13
	10c	Report details about how missing data was handled. Include rate of missing items, missing data mechanism (i.e., missing completely at random [MCAR], missing at random [MAR] or missing not at random [MNAR]) and methods used to deal with missing data (e.g., multiple imputation).	13
	10d	State how non-response error was addressed.	-
	10e	For longitudinal surveys, state how loss to follow-up was addressed.	-
	10f	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for non-	-

		representativeness of the sample.	
	10 g	Describe any sensitivity analysis conducted.	13
Results			
	11 a	Report numbers of individuals at each stage of the study. Consider using a flow diagram, if possible.	14
Respondent characteristics	11 b	Provide reasons for non-participation at each stage, if possible.	Figure 1:Study flowchart
	11 c	Report response rate, present the definition of response rate or the formula used to calculate response rate.	14
	11 d	Provide information to define how unique visitors are determined. Report number of unique visitors along with relevant proportions (e.g., view proportion, participation proportion, completion proportion).	-
Descriptive results	12	Provide characteristics of study participants, as well as information on potential confounders and assessed outcomes.	14-16, 25,26
Main findings	13 a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates along with 95% confidence intervals and p-values.	14-16, Supplementary Tabel 1-2
	13 b	For multivariable analysis, provide information on the model building process, model fit statistics, and model assumptions (as appropriate).	-
	13 c	Provide details about any sensitivity analysis performed. If there are considerable amount of missing data, report sensitivity analyses comparing the results of complete cases with that of the imputed dataset (if possible).	16
Discussion			

Limitations	14	Discuss the limitations of the study, considering sources of potential biases and imprecisions, such as non-representativeness of sample, study design, important uncontrolled confounders.	21-22
Interpretations	15	Give a cautious overall interpretation of results, based on potential biases and imprecisions and suggest areas for future research.	21-22
Generalizability	16	Discuss the external validity of the results.	22
Other sections			
Role of funding source	17	State whether any funding organization has had any roles in the survey's design, implementation, and analysis.	-
Conflict of interest	18	Declare any potential conflict of interest.	24
Acknowledgements	19	Provide names of organizations/persons that are acknowledged along with their contribution to the research.	23

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Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan

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TITLE PAGE

Association between administration or recommendation of the human papillomavirus vaccine and primary care physicians' knowledge about vaccination during proactive recommendation suspension: a nationwide cross-sectional study in Japan

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Word count 4162 words

ABSTRACT

Objective The Japanese government suspended the proactive recommendation of the human papillomavirus vaccine (HPVv) in 2013, and the vaccination rate of HPVv declined to <1% during 2014–2015. Previous studies have shown that the recommendation by a physician affects a recipient's decision to receive a vaccine, and physicians' accurate knowledge about vaccination is important to increase vaccine administration. This study aimed to evaluate the association between physicians' knowledge of vaccination and the administration or recommendation of HPVv by primary care physicians (PCPs) in the absence of proactive recommendations from the Japanese government.

Design Cross-sectional study analysed data obtained through a web-based, self-administered questionnaire survey.

Setting The questionnaire was distributed to Japan Primary Care Association (JPCA) members.

Participants JPCA members who were physicians and on the official JPCA mailing list (n=5,395) were included.

Primary and secondary outcome measures The primary and secondary outcomes were the administration and recommendation of HPVv, respectively, by PCPs. The association between PCPs' knowledge regarding vaccination and each outcome was determined based on their background and

vaccination quiz scores and a logistic regression analysis to estimate the adjusted odds ratios (AORs).

Results We received responses from 1,084 PCPs and included 981 of them in the analysis. PCPs with a higher score on the vaccination quiz were significantly more likely to administer the HPVv for routine and voluntary vaccination (AOR 2.28, 95% confidence interval [CI] 1.58–3.28; AOR 2.71, 95% CI 1.81–4.04, respectively) and recommend the HPVv for routine and voluntary vaccination than PCPs with a lower score (AOR 2.17, 95% CI 1.62–2.92; AOR 1.88, 95% CI 1.32–2.67, respectively).

Conclusions These results suggest that providing accurate knowledge regarding vaccination to PCPs may improve their administration and recommendation of HPVv, even in the absence of active government recommendations.

Strengths and limitations of this study

- This is the first study to evaluate the association between primary care physicians' (PCPs) vaccination knowledge and HPV vaccine administration and recommendation without proactive recommendation from the Japanese government.
- This nationwide study targeted the physician members of the Japan Primary Care Association, which is the largest academic society for PCPs in Japan.
- A limitation of this study was its potential selection bias due to the voluntary participation of the

PCPs in the survey.

- Furthermore, the effects of vaccine hesitancy among parents and media on the PCPs were not evaluated.

Data availability statement

Data are available from the corresponding author upon reasonable request.

Keywords: HPV vaccine; primary care physicians; administration; recommendation; vaccination

INTRODUCTION

The World Health Organization (WHO) recognises cervical cancer and other human papillomavirus (HPV)-related diseases as important global public health concerns and recommends the inclusion of HPV vaccines (HPVv) in national immunisation programmes.(1) In Japan, HPVv was introduced in 2009 as a voluntary vaccine without recommendation or funding from the government.(2, 3) In 2010, the Ministry of Health, Labour and Welfare (MHLW) initiated an urgent promotional campaign for vaccination, and the Government of Japan provided subsidies to local governments for HPVv.(2, 3) This campaign was successful, and the vaccination rate of HPVv increased to 70–80% in the targeted group of young girls in 2012.(3-6) In April 2013, free-of-charge HPV vaccination of 12- to 16-year-old girls was initiated as part of the routine vaccination programme.(3, 7, 8) On the other hand, three doses of voluntary bivalent HPVv for ≥10-year-old females and quadrivalent HPVv for ≥9-year-old females cost approximately ¥45,000 (US $450, as of April 2013). However, the media widely reported concerns regarding potential adverse effects of HPV vaccination among young girls, including complex regional pain syndrome, giving rise to social distrust and vaccine hesitancy related to HPVv.(3, 4, 7, 9) Consequently, the MHLW suspended proactive recommendation of HPV vaccination in June 2013;(7, 10) the local governments stopped sending individual notifications to the homes of girls eligible for HPVv although it continued being a part of the routine vaccine programme.(10) The HPV vaccination rate declined to less than 1% during 2014–2015.(5, 6)

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data of HPVv from 2008 to 2015 and found it to be extremely safe(11). In 2017, the GACVS expressed concerns regarding the situation in Japan, stating that the mortality rate from cervical cancer was expected to increase because HPVv was not proactively recommended.(11) In 2018, Suzuki et al. reported that there was no association between HPVv and adverse post-vaccination symptoms in Nagoya, Japan.(12) However, the MHLW did not resume the proactive recommendation of HPV vaccination as of 2019. Vaccine hesitancy has also been reported in other countries, and the WHO identified it as one of 10 threats to global health in 2019.(13)

Previous studies have shown that vaccine recommendation by a physician affects the recipient's decision in receiving a vaccine.(14-19) Thus it is important for physicians to have accurate knowledge regarding vaccination to increase vaccine administration or recommendation rates.(20-22) In Japan, the HPVv is administered not only by paediatricians, obstetricians, and gynaecologists (OBGYNs), but also by primary care physicians (PCPs).(23, 24) A 2012 nationwide survey on practices and attitudes towards vaccination among PCPs in Japan(23, 24) showed that the proportion of PCPs administering and actively recommending HPVv was 58.3% and 46.5%, respectively.(23) A significant association between PCPs' awareness of public subsidies for HPVv and recommendation of HPVv vaccination was reported.(24) As previously indicated, the government vaccination policy for the HPVv changed following the survey(23, 24), and it was expected that these proportions would also change. However, the current fraction of PCPs administering or recommending the HPVv

and the association between PCPs' knowledge about vaccination and their attitude towards HPVv in Japan remain unknown. Therefore, this study aimed to evaluate the association between PCPs' knowledge about vaccination and the administration or recommendation of HPVv without proactive recommendation by the government.

METHODS

Study design, setting, and population

This cross-sectional study analysed data obtained from a web-based, self-administered questionnaire conducted by the Preventive Medicine and Health Promotion Committee Vaccine Team of the Japan Primary Care Association (JPCA), which is the largest academic association for PCPs in Japan. Most JPCA physicians were internists working as PCPs at clinics or hospitals. The survey was conducted from March to June 2019, and the inclusion criteria were JPCA members who were physicians and on the official mailing list for JPCA members. PCPs who were junior residents within 2 years after graduation from medical school were excluded, as this group cannot administer outpatient vaccinations without the supervision of attending physicians. We excluded PCPs who lived outside Japan, were retired, employed in a non-clinical setting, or had missing data.

Patient and public involvement

There was no patient or public involvement in this study.

Questionnaire

The questionnaire items were obtained from previous questionnaires administered by the Preventive Medicine and Health Promotion Committee Vaccine Team of JPCA(23, 24) and were distributed using the online mailing list for JPCA members. The questionnaire was conducted using an online tool, SurveyMonkey. The questionnaire was self-conducted and anonymous. It collected data on the participating physicians' attitudes regarding vaccines, including HPVv (administration or recommendation), through a vaccination quiz; information resources on vaccinations; and baseline characteristics, such as sex, career after graduation, main practice category, practice setting, provision of daily paediatric medical service, population size of the main working area as an administrative unit of the local government, experience as a kindergarten or school physician, and experience raising children (details below).

Main outcome

The primary outcomes of this study were the administration of HPVv for routine and voluntary vaccination, respectively. The PCPs were asked to respond with 'yes' or 'no' to the following question: 'Do you administer routine/voluntary human papillomavirus vaccine?' Then, we investigated the association between PCPs' knowledge of vaccination and vaccine administration for each routine and voluntary vaccination, after adjusting for potential confounders (described below).

The secondary outcomes of this study were the recommendation of routine and voluntary HPV vaccination by PCPs. The respondents were asked, 'How do you recommend routine/voluntary vaccination for HPV?' The following response options were provided using a Likert-type scale: 'actively recommend', 'recommend occasionally', 'no opinion', 'do not actively recommend', and 'do not recommend'. The response 'actively recommend' was considered 'recommending behaviour', which is a more positive behaviour.(15) Furthermore, the responses 'recommend occasionally', 'no opinion', 'do not actively recommend', and 'do not recommend' were considered 'non-recommending behaviour'. Then, we investigated the association between PCPs' knowledge of vaccination and vaccine recommendation for routine and voluntary vaccination after adjusting for possible confounders (described below).

Main factor

The main factor was PCPs' knowledge of vaccination, which was assessed based on a vaccination quiz. The quiz was created by the Preventive Medicine and Health Promotion Committee Vaccine Team of the JPCA using the Delphi method.(25) The quiz comprised six general vaccine questions encompassing Japanese vaccination affairs, including a question on HPVv. Scores of 0–6 were assigned based on the number of correct answers to each of the six questions. To obtain a binary variable, we designated scores above the average as high and those below the average as low. The vaccination quiz score (high or low) was considered an independent variable.

Vaccination quiz

Q1. A 12-year-old boy has no history of mumps vaccination according to the Maternal and Child Health Handbook. His mother states that he had developed mumps in his childhood. She mentions that he had visited a clinic with bilateral parotid gland swelling, and the doctor had suspected mumps based on clinical examination without blood tests. Is it then correct to recommend a mumps vaccine to the boy? (Correct answer: correct)

Q2. A 3-month pregnant woman requests an influenza vaccine, and the only available influenza vaccine in the hospital contains thimerosal. Is this vaccine acceptable or contraindicated for this patient? (Correct answer: acceptable)

Q3. Is the 23-valent pneumococcal vaccine, an inactivated vaccine, less likely to cause swelling when injected intramuscularly than when injected subcutaneously? (Correct answer: Correct)

Q4. Is there a limit to the number of vaccines (including live vaccines) that can be concurrently administered? (Correct answer: there is no limit)

Q5. Is it correct that ‘suspending proactive recommendation of HPV vaccination’ means ‘withholding local governments from sending individual pre-vaccination screening questionnaires for HPV vaccine and notices to each household and actively calling for HPV vaccination through various media rather than the suspension of routine vaccination’? (Correct answer: correct)

Q6. Is it correct that under the 'Adverse Event Following Immunization reporting system', physicians are obligated to report to the Pharmaceuticals and Medical Devices Agency (PMDA) when a vaccinated individual begins exhibiting certain symptoms? (Correct answer: correct)

Other factors

Other factors included the physician's sex, postgraduate years (3–5, 6–10, 11–20, 21–30, 31–40, and ≥41 years), any specialist qualifications, including those related to primary care, main practice category (primary care; family physician, general practitioner, hospitalist/general physician or others; paediatricians, OBGYNs, industrial physician, researcher, administrative staff, and others), practice setting (e.g., university hospital or general hospital, other hospital, clinic, others; university, research institution, government, and health organisation), proportion of paediatric patients (number of paediatric patients with respect to the total patient population) that was high (≥10%) or low (<10%), main working area as an administrative unit of the local government in an urban area (≥50,000 people), experience as a kindergarten or school physician, experience raising children as a parent, and information resources about vaccinations (government, academic, commercial,(26) online professional community such as website/Facebook group/Twitter/JPCA mailing list,(27) and none).

Statistical analysis

We performed univariate and multivariate logistic regression analysis to estimate the odds ratios, adjusted odds ratios (AORs), and 95% confidence intervals (CIs), using binary variables for the main outcome. We investigated the association between PCPs' knowledge of vaccination and HPVv administration or recommendation.

Multiple logistic regression analysis was performed by adjusting for the following possible confounding factors: physician's sex, postgraduate year, possession of any specialist qualifications, including primary care, main practice category, practice setting, a high or low proportion of paediatric patients, experience raising children as a parent, and information resources about vaccinations.

We conducted a sensitivity analysis to inspect each variation only for HPVv knowledge (correct or incorrect) rather than for the total quiz score. We used penalized maximum likelihood logistic regression for the analyses when any confounding factors were completely separated.(28)

The analysis participants were selected after excluding participants with missing data for the main outcome, main factor, and the above-mentioned possible confounders.

All statistical analyses used two-tailed tests of significance, with significance set at $p < 0.05$.

Analyses were performed using Stata/SE 14.2 (StataCorp LLC, College Station, TX, USA).

RESULTS

Study flow and demographics

Of the 10,470 physician members of the JPCA, 5,075 who did not subscribe to JPCA mails and were, therefore, not on the mailing list were excluded. We received responses from 1,084 of 5,395 PCPs, with a response rate of 20.1%. The respondents were from all 47 prefectures of Japan. An additional 103 participants were excluded because they lived outside Japan, performed nonclinical work, or had missing data. The analysis included 981 participants (Figure 1). The median (interquartile range) score for the vaccination quiz was 4 (range, 2–5) points. The minimum and maximum scores were 0 and 6 points, respectively, and the mean (standard deviation) score was 3.47 (1.68) points. To obtain a binary variable, scores of ≥4 were designated as high, and scores of ≤3 as low. Evaluation of the participant baseline characteristics revealed that 739 (75.3%) participants were men, 358 (36.5%) had worked for 11–20 years after graduation, 420 (42.8%) worked in clinics, 719 (73.3%) worked in the urban areas, and 283 (28.9%) worked in a clinical setting where the proportion of paediatric patients was ≥10% (Table 1).

Factors associated with HPVv administration under routine vaccination

We found that 229 PCPs (23.3%) administered HPVv under routine vaccination (Table2). PCPs with higher vaccination quiz scores were significantly more likely to administer HPVv as routine vaccination than those with lower scores (AOR 2.28, 95% CI 1.58–3.28, $p < 0.001$) (Supplementary Table 1-1). There was also a positive association between the administration of routine HPV vaccination and PCPs who worked at clinics (AOR 2.64, 95% CI 1.60–4.36, $p < 0.001$), those who

had a higher proportion of paediatric patients (AOR 1.78, 95% CI 1.24–2.55, $p = 0.002$), and those who had experience as a kindergarten or school physician (AOR 2.12, 95% CI 1.45–3.10, $p < 0.001$) (Supplementary Table 1-1).

Factors associated with HPVv administration under voluntary vaccination

We found that 175 PCPs (17.8%) administered HPVv under voluntary vaccination. PCPs with higher scores on the vaccination quiz were significantly more likely to administer HPVv as voluntary vaccination than those with lower scores (AOR 2.71, 95% CI 1.81–4.04, $p < 0.001$) (Supplementary Table 1-2). There was also a positive association between administration of voluntary HPVv and PCPs who acquired information from governments (AOR 1.90, 95% CI 1.17–3.08, $p = 0.009$) and those who participated in a social network service or mailing list from an individual or group of medical service providers (AOR 1.82, 95% CI 1.25–2.64, $p = 0.002$) (Supplementary Table 1-2).

Factors associated with HPVv recommendation under routine vaccination

The PCPs selected the following options regarding the recommendation of HPVv under routine vaccination: ‘actively recommend’, 408 PCPs (41.6%); ‘recommend occasionally’, 319 PCPs (32.5%); ‘no opinion’, 181 PCPs (18.5%); ‘do not actively recommend’, 49 (5.0%); and ‘do not recommend’, 24 (2.5%) (Table 2). PCPs with higher scores on the vaccination quiz were significantly more likely to recommend HPVv under routine vaccination than those with lower

scores (AOR 2.17, 95% CI 1.62–2.92; $p < 0.001$) (Supplementary Table 2-1). However, there was a negative association between recommending routine HPV vaccination and PCPs who worked at other hospitals (AOR 0.69, 95% CI 0.48–1.00, $p = 0.048$) and clinics (AOR 0.67, 95% CI 0.46–0.98, $p = 0.041$), those who had a higher proportion of paediatric patients (AOR 0.50, 95% CI 0.36–0.70, $p < 0.001$), and those who acquired information from government sources (AOR 0.69, 95% CI 0.50–0.96, $p = 0.026$) (Supplementary Table 2-1).

Factors associated with HPVv recommendation under voluntary vaccination

The PCPs selected the following options regarding the recommendation of HPVv under voluntary vaccination: 'actively recommend', 216 PCPs (22.0%); 'recommend occasionally', 358 (36.5%); 'no opinion', 288 (29.4%); 'do not actively recommend', 75 (7.7%); and 'do not recommend', 44 (4.5%) (Table 2).

PCPs with higher vaccination quiz scores were significantly more likely to recommend HPVv under voluntary vaccination than those with low scores (AOR 1.88, 95% CI 1.32–2.67, $p < 0.001$) (Supplementary Table 2-2). There was also a positive association between the recommendation of voluntary HPV vaccination and PCPs who were male (AOR 1.67, 95% CI 1.12–2.49, $p = 0.012$) and those who participated in a social network service or mailing list for medical service from an individual or group of providers (AOR 1.56, 95% CI 1.09–2.24, $p = 0.016$). However, there was a negative association between the recommendation of voluntary HPV vaccination and PCPs who had

a higher proportion of paediatric patients (AOR 0.52, 95% CI, 0.34–0.78, $p = 0.002$) and those who had experience raising children (AOR 0.67, 95% CI 0.45–1.00, $p = 0.049$) (Supplementary Table 2-2).

The correlation coefficient between vaccine administration and recommendation for routine and voluntary HPV vaccination was 0.17 and 0.23, respectively.

Sensitivity analysis

PCPs with correct responses to the HPV vaccination quiz were significantly more likely to administer HPVv than those with incorrect responses regarding routine vaccination (AOR 2.06, 95% CI 1.38–3.09, $p < 0.001$) and voluntary vaccination (AOR 2.16, 95% CI 1.39–3.34, $p = 0.001$).

PCPs with correct responses to the HPV vaccination quiz were also significantly more likely to recommend HPV vaccination than those with incorrect responses regarding routine (AOR 1.51, 95% CI 1.12–2.04, $p = 0.006$) and voluntary vaccination (AOR 1.53, 95% CI 1.07–2.19, $p = 0.02$).

DISCUSSION

Vaccine hesitancy is a global health concern(13), and hesitancy for HPV vaccination has been reported in many countries, including Japan.(4-6) This is the first study to focus on the association between PCPs' knowledge of vaccination and their practice or attitude towards HPVv in the absence

of proactive recommendations from the government of Japan. We found positive associations between accurate vaccination knowledge among PCPs and the administration or recommendation of HPVv under routine and voluntary vaccination. In addition, the sensitivity analysis showed that physicians with accurate knowledge of HPV vaccination were likely to recommend HPVv.

A 2021 systematic review of 96 papers from 34 countries examined the perceptions, knowledge, and recommendations of healthcare providers regarding vaccines. It showed that the healthcare providers' recommendations were positively associated with their knowledge and experience, beliefs about disease risk, and perceptions of vaccine safety, necessity, and efficacy.(29) The present results are consistent with these findings.(29) In Lebanon, where HPVv is not included in the national routine vaccination schedule as of 2017, physicians practicing in obstetrics and gynaecology, paediatrics, family medicine, and infectious diseases with greater knowledge regarding HPV and HPVv recommend HPVv more often than physicians with less knowledge (AOR 3.4).(30) Further, in the United States, higher rates of completion of three HPVv doses (IRR 1.28) were observed among the patients of primary care clinicians, including family medicine physicians, paediatricians, and family and paediatric nurse-practitioners, with greater knowledge regarding HPV and HPVv (31). Our results also support these findings. Another study investigating the association between PCPs' knowledge of vaccination and the administration or recommendation of voluntary mumps vaccination for adults showed the same positive associations.(32)

Compared to that in our previous study from 2012,(23) the proportion of PCPs recommending or administering HPVv was lower in the present study: the proportion of HPVv administration decreased from 58.3% for voluntary vaccination alone(23) to 23.3% for routine vaccination and 17.8% for voluntary vaccination (Table 2). The proportion of PCPs recommending HPVv decreased from 46.5% for voluntary vaccination alone(23) to 41.6% for routine vaccination and 22.0% for voluntary vaccination (Table 2).

A study conducted among paediatricians in Osaka, Japan, in 2020 and 2021 revealed that the proportion of paediatricians who administered or actively recommended the HPVv for routine vaccination was 44.5% and 32.5% in 2020 and 67.9% and 40% in 2021, respectively.(33) In addition, a study conducted among OBGYNs in Osaka, Japan, showed that the proportion of OBGYNs recommending the HPVv for teenagers was 70.1% in 2017(3) and 84.6% in 2019.(34) As of 2018, the proportion of family physicians and paediatricians in the United States administering the HPVv was 84.1% and 95.3%, respectively,(35) and the proportion of those who strongly recommended the HPVv was 72–90% and 85–99% (11- to 12-year-old, 13- to 14-year-old, and ≥15-year-old female patients), respectively.(35) Our study revealed that in Japan, PCPs may administer routine HPVv less than paediatricians(33) and actively recommend routine HPVv more than paediatricians(33) but less than OBGYNs.(3) In addition, our study shows that Japanese PCPs may administer or recommend the HPVv less than family physicians in the United States.(35)

We also found positive associations between different information resources and administration or recommendation of voluntary HPV vaccination. Information resources from social network services or mailing lists from medical service providers seem to be positively associated with the administration or recommendation of voluntary HPV vaccination. This might be because PCPs use virtual communities as valuable knowledge portals for clinically relevant information(36) and could be interested in how and why other physicians recommend and administer vaccination.(22, 32) Government information resources were positively associated with the administration of voluntary HPVv but were negatively associated with the recommendation of routine HPVv. As of 2019, the MHLW had not resumed the proactive recommendation of routine HPV vaccination. Although the suspension of proactive recommendation was not intended to discontinue routine vaccination, it may have been misinterpreted as discontinuation of routine vaccination by some PCPs. Therefore, PCPs referring to government sources for information regarding this policy may administer HPVv as part of voluntary instead of routine vaccination and may not recommend routine HPV vaccination. Alternatively, PCPs aware of the suspension may lose confidence to recommend the HPVv. A previous study reported that the lack of government recommendations was a barrier for PCPs to recommend vaccination.(23) In November 2021, the MHLW ended this suspension and resumed proactively recommending HPV vaccination for girls born in or after the fiscal year (FY) 2006, beginning in April 2022(37), and provided ‘catch-up vaccinations’ for 3 years, from April 2022 to March 2025, for females born from FY1997 to FY2005, who became eligible for routine HPV

vaccination and may have missed the opportunity to receive the vaccination because of the suspension.(38, 39) The results of our study suggest that providing accurate knowledge and information about HPV vaccination to PCPs may help promote HPVv administration and recommendation by PCPs and thereby increase the vaccination rate. The JPCA vaccine team provides information about vaccination through websites(40) and regular onsite and online vaccine seminars for physicians.(41) Further research can help determine the optimal methods to provide accurate knowledge regarding vaccination to health care providers with vaccine hesitancy.(42)

Our study also shows that PCPs working at clinics, providing daily paediatric medical services (more than 10% of total patients), and with experience as kindergarten or school physicians tend to administer routine HPV vaccination (Supplementary Table 1). The target population for routine HPV vaccination is 12- to 16-year-old girls, and PCPs experienced in treating this group may better understand the need for routine vaccination; therefore, they may be more likely to administer the vaccine. In contrast, PCPs working at clinics or other hospitals providing daily paediatric medical services (more than 10% of total patients) were less likely to recommend routine HPV vaccination (Supplementary Table 2). In addition, PCPs providing daily paediatric medical services (more than 10% of total patients) and with experience in raising children tended to be less likely to recommend voluntary HPV vaccination (Supplementary Table 2). These results suggest that PCPs with more opportunity to provide medical service to 12- to 16-year-old girls may have less confidence to

recommend the HPVv during the suspension of proactive recommendation by the MHLW or may be more affected by the anxiousness or hesitancy of the parents.(19, 23, 43)

This study has some limitations. First, there was a potential selection bias due to the low response rate. PCPs who more actively promoted vaccination may have been more likely to respond, and the actual proportion of PCPs administering or recommending HPVv may be lower. Second, our study did not consider voluntary HPV vaccination for men. In Japan, as of 2019, the target group for both routine and voluntary HPV vaccination included only women. However, in 2020, administration of voluntary quadrivalent HPVv was approved for men. Third, our study did not evaluate 9-valent HPVv for voluntary vaccination, although in 2021, the 9-valent HPVv was approved for voluntary vaccination(44) and will be approved for routine vaccination from April 2023 onwards.(45) Future studies should include both men and women and consider the 9-valent HPVv. Fourth, we did not evaluate the effects of vaccine hesitancy among parents or mainstream media and social media on the PCPs.(43) The effect of vaccine hesitancy should be considered as one of the exposures in future studies. Fifth, we did not evaluate the effects of unknown confounding factors, which is a general limitation of observational studies. Finally, although the study participants were physician members of the JPCA, the largest society for PCPs in Japan, the generalisability of the results to PCPs outside of Japan is unclear. The policy for HPVv administration in Japan(38) changed after this study was conducted, and further surveys are needed to assess the current situation of HPVv administration and attitudes among PCPs.

Our results suggest that providing accurate knowledge regarding vaccination to PCPs may improve their administration and recommendation of the HPVv, even in the absence of active government recommendations.

CONCLUSIONS

We revealed a positive association between PCPs' knowledge of vaccines and the administration or recommendation of routine and voluntary HPV vaccination without a proactive recommendation from the government. Several factors influence PCPs' perception of HPV vaccinations, ultimately affecting public healthcare. The results of our study can be applied to other countries with similar vaccination-related concerns, such as vaccine hesitancy and disagreements on vaccine policy between the scientific community and governments.(9, 46)

Our results suggest that providing more knowledge about vaccination to PCPs may increase their likelihood to administer or recommend the HPVv, thereby improving vaccination rates.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

We obtained written informed consent from all participants before conducting the survey.

Ethics approval

The study protocol was approved by the Institutional Review Board of Osaka Medical College (Rin-763).

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TABLES

TABLE 1 Characteristics of the participants

	Participants, n=981
	n (%)
Sex: male	739 (75.3), Missing 0
Postgraduate year (y)	Missing 0
3–5	92 (9.4)
6–10	178 (18.1)
11–20	358 (36.5)
21–30	193 (19.7)
31–40	134 (13.7)
≥41	26 (2.7)
Main practice category: primary care	697 (71.1), Missing 0
Practice setting	Missing 3 (0.3)
University hospital or general hospital	281 (28.6)
Other hospital	254 (25.9)
Clinic	420 (42.8)
Others (e.g., University, research institution, government, and health organisation)	23 (2.3)
Providing daily paediatric medical service (≥ 10% of total patients)	283 (28.9), Missing 0
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	719 (73.3), Missing 2 (0.2)
Experience as kindergarten or school physician	474 (48.3), Missing 0
Experience raising children	721 (73.5), Missing 0

Main practice category: primary care: Answered main practice category as family physician or general practitioner or hospitalist/general physician

TABLE 2 Vaccination quiz scores and HPV vaccine administration or recommendation levels among primary care physicians

Vaccination quiz	Total, n (%)	Administration of HPV vaccine	Recommendation level for HPV vaccine, n (%)				
			Actively recommend	Recommend occasionally	No opinion	Do not actively recommend	Do not recommend
		Routine HPV vaccination, n=981					
		Voluntary HPV vaccination, n=981					
High scores (4–6 points)	511 (52.1)	172 (33.7)	248 (48.5)	179 (35.0)	59 (11.6)	19 (3.7)	6 (1.2)
		132 (25.8)	131 (25.6)	211 (41.3)	120 (23.5)	31 (6.1)	18 (3.5)
Low scores (0–3 points)	470 (47.9)	57 (12.1)	160 (34.0)	140 (29.8)	122 (26.0)	30 (6.4)	18 (3.8)
		43 (9.2)	85 (18.1)	147 (31.3)	168 (35.7)	44 (9.4)	26 (5.5)
Total	981 (100)	229 (23.3)	408 (41.6)	319 (32.5)	181 (18.5)	49 (5.0)	24 (2.5)
		175 (17.8)	216 (22.0)	358 (36.5)	288 (29.4)	75 (7.7)	44 (4.5)

HPV, human papillomavirus

Figure Legends

Figure 1. Study flowchart

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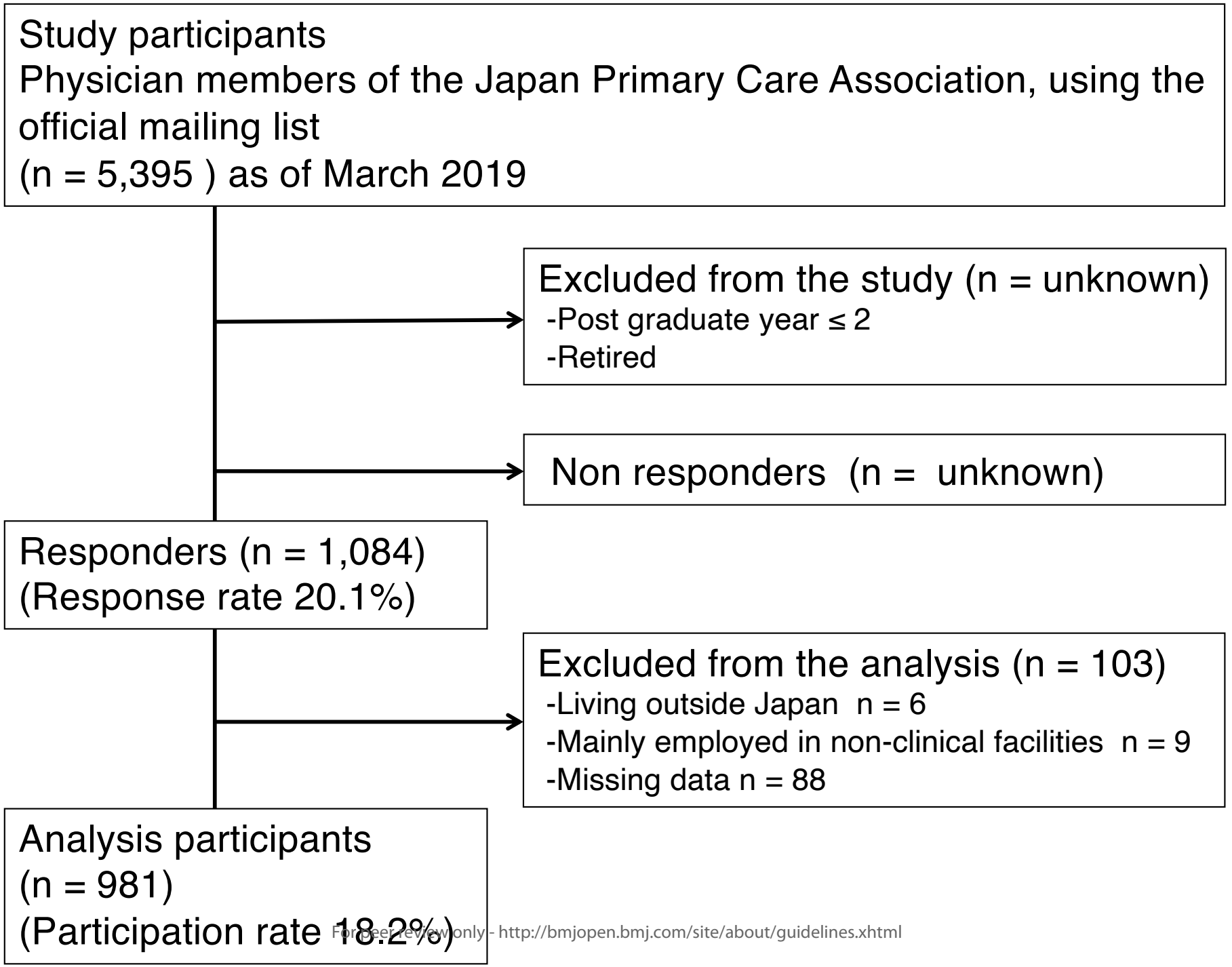

Supplementary Table 1-1 Factors associated with administration of HPV vaccine for routine vaccination

	PCPs who administer HPV vaccine, n=229 (23.3%)	PCPs who do not administer HPV vaccine, n=752 (76.7%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio* (95% CI), n=977	*p*-value
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	172 (75.1)	339 (45.1)	3.68 (2.64–5.12)	<0.001	2.28 (1.58–3.28)	<0.001
Sex: male	178 (77.7)	561 (74.6)	1.19 (0.84–1.69)	0.38	1.11 (0.75–1.65)	0.6
Postgraduate year (y)						
3-5	14 (6.1)	78 (10.4)	Reference		Reference	
6-10	28 (12.2)	150 (20.0)	1.04 (0.52–2.09)	0.91	0.48 (0.20–1.18)	0.11
11-20	95 (41.5)	263 (35.0)	2.01 (1.09–3.72)	0.026	0.83 (0.34–2.02)	0.68
21–30	51 (22.3)	142 (18.9)	2.00 (1.04–3.84)	0.037	0.91 (0.37–2.27)	0.85
31–40	34 (14.9)	100 (13.3)	1.89 (0.95–3.77)	0.069	0.80 (0.32–1.99)	0.63
≥41	7 (3.1)	19 (2.5)	2.05 (0.73–5.79)	0.17	0.79 (0.23–2.67)	0.7
Position of any specialist qualification	201 (87.8)	643 (85.6)	1.21 (0.77–1.88)	0.41	1.04 (0.57–1.89)	0.89
Main practice category: primary care	183 (79.9)	514 (68.4)	1.84 (1.29–2.63)	0.001	1.18 (0.74–1.88)	0.5
Practice setting						
University hospital or general hospital	28 (12.2)	253 (33.8)	Reference		Reference	
Other hospital	35 (15.3)	219 (29.2)	1.44 (0.85–2.45)	0.17	1.18 (0.68–2.06)	0.55
Clinic	164 (71.6)	256 (34.2)	5.79 (3.74–8.96)	<0.001	2.64 (1.60–4.36)	<0.001
Others (i.e., University, research institution, government, and health organisation)	2 (0.87)	21 (2.8)	0.86 (0.19–3.86)	0.85	0.90 (0.22–3.73)	0.88
Providing daily paediatric medical service (≥ 10% of total patients)	113 (49.3)	170 (22.6)	3.33 (2.45–4.55)	<0.001	1.78 (1.24–2.55)	0.002
Mainly working in an urban area (≥ 50,000 people as an administrative unit of the local government)	164 (71.6)	555 (74.0)	0.89 (0.64–1.23)	0.48	1.07 (0.73–1.55)	0.74
Experience as kindergarten or school physician	165 (72.1)	309 (41.1)	3.70 (2.68–5.11)	<0.001	2.12 (1.45–3.10)	<0.001
Experience raising children	176 (76.9)	545 (72.5)	1.26 (0.89–1.78)	0.19	0.86 (0.56–1.32)	0.48
Information resource						
Government	189 (82.5)	558 (74.2)	1.64 (1.13–2.40)	0.01	1.25 (0.82–1.90)	0.29
Academia	226 (98.7)	687 (91.4)	7.13 (2.22–22.90)	0.001	1.76 (0.55–5.64)	0.34
Commerce	71 (31.0)	212 (28.2)	1.14 (0.83–1.58)	0.41	0.85 (0.58–1.23)	0.38
Social network service or mailing list by individuals or group of medical service providers	94 (41.1)	205 (27.3)	1.86 (1.36–2.53)	<0.001	1.26 (0.88–1.80)	0.21
None	0	19 (2.5)	0.08 (0.05–1.36)*	0.081	0.35 (0.02–8.24)	0.52

*Penalized maximum likelihood logistic regression. PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Supplementary Table 1-2 Factors associated with administration of HPV vaccine for voluntary vaccination

	PCPs who administer HPV vaccine, n=175 (17.8%)	PCPs who do not administer HPV vaccine, n=806 (82.2%)	Crude odds ratio (95% CI), n=981	*p*-value	Adjusted odds ratio* (95% CI), n=977	*p*-value
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	132 (75.4)	379 (47.0)	3.46 (2.39–5.01)	<0.001	2.71 (1.81–4.04)	<0.001
Sex: male	131 (74.8)	608 (75.4)	0.97 (0.66–1.41)	0.87	0.89 (0.59–1.35)	0.58
Postgraduate year (y)						
3-5	12 (6.9)	80 (9.9)	Reference		Reference	
6-10	21 (12.0)	157 (19.5)	0.89 (0.42–1.90)	0.77	0.48 (0.19–1.23)	0.13
11-20	66 (37.7)	292 (36.2)	1.51 (0.78–2.92)	0.23	0.69 (0.27–1.75)	0.43
21–30	41 (23.4)	152 (18.9)	1.80 (0.89–3.61)	0.099	0.97 (0.38–2.50)	0.96
31–40	28 (16.0)	106 (13.2)	1.76 (0.84–3.67)	0.13	0.98 (0.38–2.53)	0.97
≥41	7 (4.0)	19 (2.4)	2.46 (0.85–7.07)	0.096	1.35 (0.40–4.57)	0.63
Position of any specialist qualification	154 (88.0)	690 (85.7)	1.22 (0.74–2.01)	0.43	1.12 (0.59–2.12)	0.73
Main practice category: primary care	141 (80.6)	556 (69.0)	1.86 (1.25–2.79)	0.002	1.52 (0.93–2.49)	0.098
Practice setting						
University hospital or general hospital	36 (20.6)	245 (30.5)	Reference		Reference	
Other hospital	29 (16.6)	225 (28.0)	0.89 (0.52–1.48)	0.62	0.68 (0.39–1.19)	0.18
Clinic	109 (62.3)	311 (38.7)	2.39 (1.58–3.60)	<0.001	1.27 (0.77–2.08)	0.35
Others (i.e., University, research institution, government, and health organisation)	1 (0.57)	22 (2.7)	0.31 (0.04–2.37)	0.26	0.37 (0.06–2.10)	0.26
Providing daily paediatric medical service (≥ 10% of total patients)	66 (37.7)	217 (26.9)	1.64 (1.17–2.32)	0.005	1.04 (0.70–1.55)	0.84
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	135 (77.1)	584 (72.6)	1.27 (0.86–1.87)	0.22	1.26 (0.83–1.91)	0.27
Experience as kindergarten or school physician	106 (60.6)	368 (45.7)	1.83 (1.31–2.55)	<0.001	1.23 (0.82–1.84)	0.31
Experience raising children	129 (73.7)	592 (73.5)	1.01 (0.70–1.47)	0.07	0.70 (0.45–1.08)	0.11
Information resource						
Government	152 (86.9)	595 (73.8)	2.34 (1.47–3.73)	<0.001	1.90 (1.17–3.08)	0.009
Academia	170 (97.1)	743 (92.2)	2.88 (1.14–7.28)	0.025	0.93 (0.35–2.43)	0.88
Commerce	55 (31.4)	228 (28.3)	1.16 (0.82–1.66)	0.41	0.84 (0.57–1.25)	0.39
Social network service or mailing list by individuals or group of medical service providers	80 (45.7)	219 (27.2)	2.26 (1.61–3.16)	<0.001	1.82 (1.25–2.64)	0.002
None	0	19 (2.4)	0.12 (0.01–1.91)*	0.13	0.39 (0.02–8.00)	0.54

*Penalized maximum likelihood logistic regression. PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Supplementary Table 2-1 Factors associated with recommendation of HPV vaccine for routine vaccination

	PCPs who recommend HPV vaccine, n=408 (41.6%)	PCPs who do not recommend HPV vaccine, n=573 (58.4%)	Crude odds ratio (95% CI), n=981	*p* -value	Adjusted odds ratio (95% CI), n=977	*p* -value
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	248 (60.8)	263 (45.9)	1.83 (1.41–2.36)	<0.001	2.17 (1.62–2.92)	<0.001
Sex: male	319 (78.2)	420 (73.3)	1.31 (0.97–1.76)	0.08	1.37 (0.99–1.90)	0.056
Postgraduate year (y)						
3-5	44 (10.8)	48 (8.4)	Reference		Reference	
6-10	69 (16.9)	109 (19.0)	0.69 (0.42–1.15)	0.15	0.89 (0.47–1.68)	0.72
11-20	153 (37.5)	205 (35.8)	0.81 (0.51–1.29)	0.38	1.03 (0.53–1.99)	0.94
21–30	90 (22.1)	103 (18.0)	0.95 (0.58–1.57)	0.85	1.28 (0.64–2.53)	0.48
31–40	45 (11.0)	89 (15.5)	0.55 (0.32–0.95)	0.032	0.73 (0.36–1.48)	0.38
≥41	7 (1.7)	19 (3.3)	0.40 (0.15–1.05)	0.062	0.56 (0.19–1.62)	0.28
Position of any specialist qualification	347 (85.1)	497 (86.9)	0.86 (0.60–1.24)	0.41	0.79 (0.49–1.29)	0.35
Main practice category: primary care	281 (68.9)	416 (72.6)	0.84 (0.63–1.10)	0.21	0.79 (0.55–1.11)	0.18
Practice setting						
University hospital or general hospital	143 (33.8)	143 (25.1)	Reference		Reference	
Other hospital	101 (24.8)	219 (29.2)	0.68 (0.49–0.96)	0.03	0.69 (0.48–1.00)	0.048
Clinic	161 (39.5)	259 (45.4)	0.64 (0.47–0.87)	0.005	0.67 (0.46–0.98)	0.041
Others (e.g., University, research institution, government, and health organisation)	8 (2.0)	15 (2.6)	0.55 (0.23–1.34)	0.19	0.51 (0.20–1.31)	0.16
Providing daily paediatric medical service (≥10% of total patients)	95 (23.3)	188 (32.8)	0.62 (0.47–0.83)	0.001	0.50 (0.36–0.70)	<0.001
Mainly working in an urban area (≥ 50,000 people as an administrative unit of the local government)	305 (74.9)	414 (72.4)	1.14 (0.85–1.52)	0.37	1.08 (0.78–1.47)	0.65
Experience as kindergarten or school physician	190 (46.6)	284 (49.6)	0.89 (0.69–1.14)	0.36	1.09 (0.80–1.49)	0.57
Experience raising children	296 (72.6)	425 (74.2)	0.92 (0.69–1.23)	0.57	0.79 (0.56–1.10)	0.16
Information resource						
Government	294 (72.1)	453 (79.1)	0.68 (0.51–0.92)	0.011	0.69 (0.50–0.96)	0.026
Academia	385 (94.4)	528 (92.2)	1.43 (0.85–2.40)	0.18	1.21 (0.63–2.35)	0.56
Commerce	113 (27.7)	170 (29.7)	0.91 (0.69–1.20)	0.5	0.91 (0.67–1.25)	0.56
Social network service or mailing list by individuals or group of medical service providers	136 (33.3)	163 (28.5)	1.26 (0.96–1.65)	0.1	1.33 (0.98–1.82)	0.071
None	7 (1.7)	12 (2.1)	0.82 (0.32–2.09)	0.67	0.82 (0.25–2.68)	0.74

PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Supplementary Table 2-2 Factors associated with recommendation of HPV vaccine for voluntary vaccination

	PCPs who recommend HPV vaccine, n=216 (22.0%)	PCPs who do not recommend HPV vaccine, n=765 (78.0%)	Crude odds ratio (95% CI), n=981	*p* -value	Adjusted odds ratio (95% CI), n=977	*p* -value
Factors	n (%)	n (%)				
High scores on vaccination quiz (4–6 points)	131 (60.6)	380 (49.7)	1.56 (1.15–2.12)	0.005	1.88 (1.32–2.67)	<0.001
Sex: male	174 (80.6)	565 (73.9)	1.47 (1.01–2.13)	0.045	1.67 (1.12–2.49)	0.012
Postgraduate year (y)						
3-5	24 (11.1)	68 (8.9)	Reference		Reference	
6-10	30 (13.9)	148 (19.4)	0.57 (0.31–1.06)	0.074	0.81 (0.37–1.75)	0.59
11-20	87 (40.3)	271 (35.4)	0.91 (0.54–1.54)	0.72	1.40 (0.63–3.08)	0.41
21–30	52 (24.1)	141 (18.4)	1.04 (0.59–1.84)	0.88	1.73 (0.77–3.88)	0.19
31–40	21 (9.7)	113 (14.8)	0.53 (0.27–1.02)	0.056	0.84 (0.36–1.98)	0.69
≥41	2 (0.9)	24 (3.1)	0.24 (0.05–1.02)	0.062	0.38 (0.07–1.89)	0.24
Position of any specialist qualification	184 (85.2)	660 (86.4)	0.91 (0.59–1.39)	0.65	0.74 (0.40–1.35)	0.32
Main practice category: primary care	148 (68.5)	549 (71.7)	0.86 (0.62–1.19)	0.35	0.84 (0.55–1.27)	0.4
Practice setting						
University hospital or general hospital	81 (37.5)	200 (26.3)	Reference		Reference	
Other hospital	53 (24.5)	201 (26.4)	0.65 (0.44–0.97)	0.03	0.69 (0.45–1.06)	0.091
Clinic	77 (35.7)	343 (45.0)	0.55 (0.39–0.79)	0.001	0.67 (0.43–1.04)	0.075
Others (e.g., University, research institution, government, and health organisation)	5 (2.3)	18 (2.4)	0.69 (0.25–1.91)	0.47	0.63 (0.21–1.84)	0.4
Providing daily paediatric medical service (≥10% of total patients)	43 (19.9)	240 (31.4)	0.54 (0.38–0.78)	0.001	0.52 (0.34–0.78)	0.002
Mainly working in an urban area (≥50,000 people as an administrative unit of the local government)	171 (80.0)	547 (71.6)	1.59 (1.10–2.30)	0.014	1.42 (0.95–2.11)	0.084
Experience as kindergarten or school physician	87 (40.3)	387 (50.6)	0.66 (0.48–0.90)	0.008	0.79 (0.55–1.14)	0.21
Experience raising children	153 (70.8)	568 (74.3)	0.84 (0.60–1.18)	0.32	0.67 (0.45–1.00)	0.049
Information resource						
Government	155 (71.8)	592 (77.4)	0.74 (0.53–1.04)	0.087	0.80 (0.55–1.16)	0.24
Academia	202 (93.5)	711 (92.9)	1.10 (0.60–2.01)	0.77	0.94 (0.44–2.04)	0.88
Commerce	60 (27.8)	223 (29.2)	0.93 (0.67–1.31)	0.69	0.91 (0.63–1.32)	0.62
Social network service or mailing list by individuals or group of medical service providers	79 (36.6)	220 (28.8)	1.43 (1.04–1.96)	0.028	1.56 (1.09–2.24)	0.016
None	4 (1.9)	15 (2.0)	0.94 (0.31–2.87)	0.92	0.84 (0.21–3.40)	0.81

PCPs, primary care physicians; HPV, human papillomavirus; CI, confidence interval

Checklist for Reporting Of Survey Studies (CROSS)

Section/topic	Item	Item description	Reported on page #
Title and abstract			
Title and abstract	1a	State the word "survey" along with a commonly used term in title or abstract to introduce the study's design.	3
	1b	Provide an informative summary in the abstract, covering background, objectives, methods, findings/results, interpretation/discussion, and conclusions.	3-4
Introduction			
Background	2	Provide a background about the rationale of study, what has been previously done, and why this survey is needed.	6-8
Purpose/aim	3	Identify specific purposes, aims, goals, or objectives of the study.	8
Methods			
Study design	4	Specify the study design in the methods section with a commonly used term (e.g., cross-sectional or longitudinal).	8-9
Data collection methods	5a	Describe the questionnaire (e.g., number of sections, number of questions, number and names of instruments used).	9
	5b	Describe all questionnaire instruments that were used in the survey to measure particular concepts. Report target population, reported validity and reliability information, scoring/classification procedure, and reference links (if any).	9
	5c	Provide information on pretesting of the questionnaire, if performed (in the article or in an online supplement).	-

		Report the method of pretesting, number of times questionnaire was pre-tested, number and demographics of participants used for pretesting, and the level of similarity of demographics between pre-testing participants and sample population.	
	5d	Questionnaire if possible, should be fully provided (in the article, or as appendices or as an online supplement).	-
	6a	Describe the study population (i.e., background, locations, eligibility criteria for participant inclusion in survey, exclusion criteria).	8-9
Sample characteristics	6b	Describe the sampling techniques used (e.g., single stage or multistage sampling, simple random sampling, stratified sampling, cluster sampling, convenience sampling). Specify the locations of sample participants whenever clustered sampling was applied.	9
	6c	Provide information on sample size, along with details of sample size calculation.	-
	6d	Describe how representative the sample is of the study population (or target population if possible), particularly for population-based surveys.	-
Survey administration	7a	Provide information on modes of questionnaire administration, including the type and number of contacts, the location where the survey was conducted (e.g., outpatient room or by use of online tools, such as SurveyMonkey).	9
	7b	Provide information of survey's time frame, such as periods of recruitment, exposure, and follow-up days.	8
	7c	Provide information on the entry process: –>For non-web-based surveys, provide approaches to	-

		minimize human error in data entry. –>For web-based surveys, provide approaches to prevent "multiple participation" of participants.	
Study preparation	8	Describe any preparation process before conducting the survey (e.g., interviewers' training process, advertising the survey).	-
Ethical considerations	9a	Provide information on ethical approval for the survey if obtained, including informed consent, institutional review board [IRB] approval, Helsinki declaration, and good clinical practice [GCP] declaration (as appropriate).	23
	9b	Provide information about survey anonymity and confidentiality and describe what mechanisms were used to protect unauthorized access.	9
Statistical analysis	10a	Describe statistical methods and analytical approach. Report the statistical software that was used for data analysis.	13
	10b	Report any modification of variables used in the analysis, along with reference (if available).	13
	10c	Report details about how missing data was handled. Include rate of missing items, missing data mechanism (i.e., missing completely at random [MCAR], missing at random [MAR] or missing not at random [MNAR]) and methods used to deal with missing data (e.g., multiple imputation).	13
	10d	State how non-response error was addressed.	-
	10e	For longitudinal surveys, state how loss to follow-up was addressed.	-
	10f	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for non-	-

		representativeness of the sample.	
	10 g	Describe any sensitivity analysis conducted.	13
Results			
	11 a	Report numbers of individuals at each stage of the study. Consider using a flow diagram, if possible.	14
Respondent characteristics	11 b	Provide reasons for non-participation at each stage, if possible.	Figure 1:Study flowchart
	11 c	Report response rate, present the definition of response rate or the formula used to calculate response rate.	14
	11 d	Provide information to define how unique visitors are determined. Report number of unique visitors along with relevant proportions (e.g., view proportion, participation proportion, completion proportion).	-
Descriptive results	12	Provide characteristics of study participants, as well as information on potential confounders and assessed outcomes.	14-16, 25,26
Main findings	13 a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates along with 95% confidence intervals and p-values.	14-16, Supplementary Tabel 1-2
	13 b	For multivariable analysis, provide information on the model building process, model fit statistics, and model assumptions (as appropriate).	-
	13 c	Provide details about any sensitivity analysis performed. If there are considerable amount of missing data, report sensitivity analyses comparing the results of complete cases with that of the imputed dataset (if possible).	16
Discussion			

Limitations	14	Discuss the limitations of the study, considering sources of potential biases and imprecisions, such as non-representativeness of sample, study design, important uncontrolled confounders.	21-22
Interpretations	15	Give a cautious overall interpretation of results, based on potential biases and imprecisions and suggest areas for future research.	21-22
Generalizability	16	Discuss the external validity of the results.	22
Other sections			
Role of funding source	17	State whether any funding organization has had any roles in the survey's design, implementation, and analysis.	-
Conflict of interest	18	Declare any potential conflict of interest.	24
Acknowledgements	19	Provide names of organizations/persons that are acknowledged along with their contribution to the research.	23