American Journal of Preventive Medicine

RESEARCH ARTICLE

Determinants of Human Papillomavirus Vaccine Uptake by Adult Women Attending Cervical Cancer Screening in 9 European Countries



Claudia Robles, PhD,¹ Laia Bruni, PhD,¹ Amelia Acera, PhD,^{2,3} Joan Carles Riera, PhD,⁴ Laia Prats, MD,⁵ Mario Poljak, PhD,⁶ Jana Mlakar, PhD,⁶ Anja Oštrbenk Valenčak, PhD,⁶ Tiina Eriksson, MSc, Matti Lehtinen, PhD, Karolina Louvanto, PhD, Maria Hortlund, MSc, Joakim Dillner, PhD, Mette T. Faber, PhD, Christian Munk, PhD, Susanne K. Kjaer, DMSc, 10,11 Karl Ulrich Petry, PhD, ¹² Agnieszka Denecke, MD, ¹² Lan Xu, MSc, ¹³ Marc Arbyn, PhD, ¹³ Louise Cadman, BSc, 14 Jack Cuzick, PhD, 14 Véronique Dalstein, PhD, 15 Christine Clavel, PhD, 15 Silvia de Sanjosé, PhD, 16,17 F. Xavier Bosch, PhD 1,18

Introduction: Human papillomavirus-vaccinated cohorts, irrespective of age, will likely reduce their subsequent screening requirements, thus opening opportunities for global cost reduction and program sustainability. The determinants of uptake and completion of a 3-dose human papillomavirus vaccination program by adult women in a European context were estimated.

Study design: This was an intervention study.

Setting/participants: Study participants were women aged 25–45 years, attending opportunistic or population-based cervical cancer screening in Belgium, Denmark, Finland, France, Germany, Slovenia, Spain, Sweden, and the United Kingdom between April 2016 and May 2018.

Intervention: Study participants completed a questionnaire on awareness and attitudes on adult female human papillomavirus vaccination and were invited to receive free human papillomavirus vaccination.

Main outcome measures: Main outcome measures were acceptance, uptake, and completion of vaccination schedule. Determinants of vaccine uptake were explored using multilevel logistic models in 2019.

Results: Among 3,646 participants, 2,748 (range by country=50%-96%) accepted vaccination, and 2,151 (range=30%-93%) received the full vaccination course. The factors associated with

From the ¹Cancer Epidemiology Research Programme, IDIBELL, Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain; ²Atenció a la Salut Sexual i Reproductiva (ASSIR) SAP Cerdanyola-Ripollet, Institut Catala de la Salut, Barcelona, Spain; ³Unitat de Suport a la Recerca Metropolitana Nord, IDIAP Jordi Gol, Barcelona, Spain; ⁴Atenció a la Salut Sexual i Reproductiva (ASSIR) SAP Girones-Pla de l'Estany, Institut Catala de la Salut, Girona, Spain; ⁵Centre Ginecològic Gine-3, Barcelona, Spain; ⁶Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; ⁷Department of Health Science, University of Tampere, Tampere, Finland; ⁸Department of Obstetrics and Gynecology, University of Tampere, Tampere, Finland; ⁹Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; ¹⁰Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; ¹¹Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ¹²Department of Gynecologic Oncology, Klinikum Wolfsburg, Wolfsburg, Germany; 13Unit of Cancer Epidemiology, Belgian Cancer Centre,

Sciensano, Brussels, Belgium; 14Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom; 15 Centre Hospitalier Universitaire (CHU) Reims, Université de Reims Champagne-Ardenne INSERM P3Cell and UMR-S 1250, SFR CAP-SANTE, Reims, France; ¹⁶PATH, Seattle, Washington; 17 Centro de Investigación Biomédica en Red en Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain; and ¹⁸Faculty of Health Sciences, Universitat Oberta de Catalunya (UOC), Barcelona, Spain

Address correspondence to: Claudia Robles, PhD, Unit of Infections and Cancer-Information and Interventions (UNIC-I&I), Cancer Epidemiology Research Programme, IDIBELL, Catalan Institute of Oncology, L' Hospitalet de Llobregat, Avenue Gran Via 199-203, 08908 Barcelona, Spain. E-mail: crobles@idibell.cat.

0749-3797/\$36.00

https://doi.org/10.1016/j.amepre.2020.08.032

higher vaccine acceptance were previous awareness of adult female (OR=1.22, 95% CI=1.00, 1.48) and male (OR=1.59, 95% CI=1.28, 1.97) vaccination. Women in stable relationships (OR=0.56, 95% CI=0.45, 0.69) or with higher educational level (OR=0.76, 95% CI=0.63, 0.93) were more likely to refuse vaccination. Recruitment by postal invitation versus personal invitation from a healthcare professional resulted in lower vaccine acceptance (OR=0.13, 95% CI=0.02, 0.76). Vaccination coverage of >70% of adolescent girls in national public programs was of borderline significance in predicting human papillomavirus vaccine uptake (OR=3.23, 95% CI=0.95, 10.97). The main reasons for vaccine refusal were vaccine safety concerns (range=30%—59%) and the need for more information on human papillomavirus vaccines (range=1%—72%). No safety issues were experienced by vaccinated women.

Conclusions: Acceptance and schedule completion were largely dependent on recruitment method, achieved coverage of national vaccination programs, and personal relationship status. Knowledge of benefits and safety reassurance may be critical to expanding vaccination target ages. Study results suggest that there are no major opinion barriers in adult women to human papillomavirus vaccination, especially when vaccination is offered face to face in healthcare settings.

Trial Registration: EudraCT Number 2014-003177-42.

Am J Prev Med 2021;60(4):478–487. © 2020 American Journal of Preventive Medicine. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

INTRODUCTION

ervical cancer is an important health problem in Europe with about 60,000 new cases and 25,000 deaths per year.¹ The highest burdens are observed in Central and Eastern Europe,¹ which can largely be ascribed to the absence of screening, historical differences in coverage, quality of national screening programs, or differences in human papillomavirus (HPV) exposure.^{2,3}

Novel methods for cervical cancer detection include clinically validated HPV tests. These show a higher sensitivity and negative predictive values than cytology. ^{4,5} Furthermore, they are processed by automatic or semi-automatic instruments, which increases throughput, eliminates the subjectivity of cytology, and enhances program quality assurance. ⁶

Although initially indicated for adolescent girls only, HPV vaccines continue to expand their licensing, clinical indications, and dosing regimens. These include vaccination of both male and female individuals aged >40 years, vaccination of immunocompromised groups, vaccination at the time of treatment of cervical intraepithelial neoplasia Grades 2 and 3 and adenocarcinoma in situ, vaccination for recurrent respiratory papillomatosis cases, and 2-dose regimens in those aged <15 years. However, national programs are mainly offering vaccination to a few cohorts of adolescent girls per year.

The HPV-FASTER strategy proposes programs including an HPV screening visit and treatment if required, in combination with broad-spectrum HPV

vaccination to adult women. ¹² This could facilitate better detection and early intervention against prevalent disease and protection against future infection. These interventions should potentially reduce subsequent screening needs. However, this strategy is not free of uncertainties. These include vaccine acceptance by adult women, safety, and reduced effectiveness compared with those among younger women. ^{7,13} Currently, European Union vaccine licensing does not include an upper age limit, ¹⁴ – ¹⁶ and the U.S. Food and Drug Administration recently extended the upper limit to age 45 years. ^{17,18} However, to date, no formal recommendations to expand target ages for vaccination beyond age 26 years have been issued.

Only a few highly heterogeneous studies on willingness to have HPV vaccination among the adult population have been conducted in Europe, where uptake remains anecdotal. To the best of the authors' knowledge, no study in adult women has explored how HPV vaccination could be integrated with screening, and none have assessed uptake and completion rates of the full 3-dose schedule.

Comparing Health Services Interventions for the Prevention of HPV-Related Cancer project (COHEAHR) is a European Union—funded consortium investigating the opportunities for cervical cancer prevention by means of strategic protocols of HPV screening and vaccination (www.coheahr.eu). Within this project, COHEAHR-WP4 is a multinational study conducted in 9 European countries (Belgium, Denmark, Finland, France, Germany, Slovenia, Spain, Sweden, and the United

Kingdom [UK]) aimed to identify global and regional determinants of HPV vaccine acceptability and completion rates as well as logistics and programmatic issues of vaccinating adult women attending routine cervical cancer screening.

METHODS

Study Population

Intended recruitment per country was 250-300 women aged 25-45 years (age range varying by country) and not previously vaccinated against HPV. Spain was to recruit an additional 150 underscreened women (i.e., not screened in the last 5 years). Participants self-completed a questionnaire on sociodemographics, medical history, attitude toward screening, awareness and opinion on HPV vaccine, and vaccine acceptability. They were also asked to select from predefined answers, those relevant to their decision on vaccine acceptability or to complete an open field question (Appendix Text 1, available online). Those who accepted vaccination and were eligible were offered free vaccination except in the UK, where HPV vaccine could not be administered owing to ongoing changes in the call-recall system of the cervical cancer screening program affecting planned population-based recruitment. Participants were followed for a 6-month period for completion of the 3-dose vaccine schedule and safety data collection. Noneligibility criteria for HPV vaccination included current or planned pregnancy within the following months, allergy or hypersensitivity to any vaccine component, history of immune disease, or hysterectomy. HPV vaccination was also offered to women unwilling to complete the questionnaire. HPV vaccines used in the study were provided at no cost by GlaxoSmithKline Biologicals SA (Cervarix) and Sanofi Pasteur MSD (Gardasil and Gardasil9, whose current Marketing Authorization Holder is Merck Sharp and Dohme). The choice of vaccine used in each country was based on existing national priorities in their public programs.

Each country used the same core protocol and data collection forms, but each national coordinator chose the strategy to recruit and vaccinate adult women that would best fit the existing screening efforts in their country (Table 1). Participating countries with population-based cervical cancer screening programs (Denmark and Sweden) invited women to participate in the study as if they were invited to get screened (population-based approach). On the basis of age and place of residency, potentially eligible women were identified using screening or census registries and invited through postal letters that included the questionnaire. Therefore, the randomly selected population potentially included noneligible women already vaccinated or pregnant, breastfeeding, or planning to become pregnant soon. Eligible women were asked to return the completed questionnaire and, if they accepted vaccination, to arrange a visit at a vaccination center. The remaining countries with opportunistic screening and the UK used convenience recruitment by inviting women attending healthcare or screening services for cervical screening through brochures, posters, healthcare providers, or phone calls to recently screened women. If not available, recruitment sites were provided with fridges, thermometers, and protocols for vaccine storage and temperature control. Germany invited HPV-screened women included in the

Wolfsburg pilot project for better cervical cancer prevention with primary HPV screening. A Recruitment took place between April 2016 and May 2018. The inclusion of 250–300 women per country allowed estimating acceptance, uptake, and completion rate with a minimum precision of $\pm 6.2\%$.

Ethical approvals were obtained by local IRBs and the Ministry of Health, where applicable. All participants provided free and written informed consent.

Measures

Irrespective of recruitment method, study participants were defined as women who either completed the questionnaire or accepted vaccination without completion of the questionnaire. Study vaccination outcomes were estimated for (1) acceptance (proportion of women willing to be vaccinated in the questionnaire), (2) uptake (proportion of women who actually were vaccinated), and (3) completion rate (proportion of women who completed the 3-dose vaccine schedule).

Statistical Analysis

The heterogeneity observed between study sites (Table 1) and participant characteristics (Appendix Table 1, available online) were used to explore the effect of context and individual factors on vaccine uptake. The main characteristics assessed at the site level included the recruitment method (population-based versus convenience) and the national or regional immunization program characteristics obtained from published reports.²⁵⁻³³ Included were vaccination coverage in targeted adolescent girls categorized as low (<50%) or high (>70%); whether catch-up vaccination campaigns had been conducted in the country, suggesting that target participants might have already been offered HPV vaccination; and whether the country had already implemented male vaccination programs. Individual characteristics included age (in quintiles), being in a stable relationship, foreign-born status, education level, and knowledge of HPV vaccine (ever heard of it and aware of the eligibility of adult women and boys for HPV vaccination).

Among women completing the questionnaire, the effect of individual and site characteristics on vaccine uptake was explored using stepwise-multilevel logistic regression analysis with individuals (first level) nested within sites (second level).³⁴ Model A incorporated only site-specific random effects to model variation in vaccine uptake between sites by means of intraclass correlation on the basis of the latent response formulation.³⁵ The intraclass correlation assesses the individuals' variation in vaccine uptake at the site level so that values close to 0% inform a very low or null effect of site on vaccine uptake. Model B included individual covariates to explore the potential association of individual-level variables, and Model C additionally included the contextual variables. Results are reported as AORs with 95% CIs as well as predicted probabilities.

Statistical significance was set at p<0.05, and statistical analyses were carried out using Stata, version 15.1, and R, version 3.2.3. Analyses were conducted in 2019.

RESULTS

Response rates (including completed questionnaires or reasons for nonparticipation) in the 2 countries with a population-based approach were 34.4% of 1,932 invitations in

Table 1. Study Site Characteristics by Country

Country	Ages, years	HPV vaccine	Recruitment	Source	Invitation	National immunization program characteristics ^a		
						Coverage targeted girls, %	Catch-up campaign	Boys vaccination
Belgium	25-45	2HPVv	Convenience	OB/GYN public practice (Ghent and Brussels)	On-site brochures, HCP criteria	>70 and <50	Yes	No
Denmark	30–45	4HPVv	Pop based	Screening registry (Greater Copenhagen area)	Postal letter	<50	Yes	No
Finland	25–35	2HPVv 9HPVv	Convenience	Screening sites (Rauma, Kuopio, Helsinki, and Tampere)	On-site brochures, HCP criteria, phone calls	>70	Yes ^b	Yes ^b
France	25-45	4HPVv	Convenience	OB/GYN public practice (Reims)	HCP criteria	<50	Yes	No
Germany	25–45	4HPVv	Convenience	Wolfsburg pilot project OB/GYN private practices (n=80)	WOLPHSCREEN participants	<50	Yes	Yes
Slovenia	25–45	9HPVv	Convenience	OB/GYN public practice (Litija and Nova Gorica)	HCP criteria	<50	No	No
Spain	25-45	2HPVv 9HPVv	Convenience	OB/GYN public practices (Cerdanyola and Girona) and private practice (Barcelona)	HCP criteria	>70	No	No
Sweden	25–45	9HPVv	Pop based	Population registry (Stockholm county)	Postal letter	>70	Yes	No
UK	30–45	NA ^c	Convenience	England GP practices (n=253)	Posters with link to an online questionnaire	>70	Yes	No

aNational immunization program characteristics were obtained from certain sources. 25-33 Coverage targeted girls refers to the achieved HPV vaccination coverage achieved during the study recruitment period in young girls/Catch-up campaign refers to the potential targeting of study participants in previous catch-up campaigns/Boys vaccination refers to the implementation of HPV vaccination. in boys within the national immunization program at the time of the study.

2HPVv, bivalent vaccine (Cervarix); 4HPVv, quadrivalent vaccine (Gardasil); 9HPVv, nonavalent vaccine (Gardasil 9); GP, general practitioner; HCP, healthcare providers; HPV, human papillomavirus; NA, not applicable; OB/GYN, Obstetrics/Gynecology; UK, United Kingdom; WOLPHSCREEN, Wolfsburg pilot project for better prevention of cervical cancer with primary HPV screening.

bln the participating sites in Finland, women and men might have been targeted and vaccinated as part of a large cluster-randomized trial.

^cNA because UK conducted a questionnaire-only study.

Denmark and 17.3% of 2,962 invitations in Sweden (Appendix Figure 1, available online).

In all countries, 4,137 women replied to the invitation, 328 refused to participate, and 161 completed the questionnaire despite already being vaccinated and therefore ineligible. In total, 3,648 eligible women participated in the study (Table 2), 9 of whom only participated in the vaccination component.

All recruiting countries achieved or surpassed their recruitment target except France owing to clinic workload and recruitment overestimation.

The HPV vaccine was accepted by 2,748 women (range by country=50%-96%) (Table 2). Among study participants, 20 acceptors and 151 refusers of vaccination were ineligible for vaccination. Reasons for not getting vaccinated among acceptors were not collected. However, in countries with convenience sampling, uptake was only slightly lower than acceptance rates where vaccination was scheduled for a date different from that of study invitation (50%-93% uptake). In Denmark and Sweden, 19 (9.9%) and 78 (40.2%), respectively, women who accepted vaccination in the questionnaire did not schedule an appointment for vaccine administration. By age, vaccine uptake was higher among women aged <30 years (78.4% vs 67.5%).

In multivariate multilevel analysis (Table 3), lower uptake was observed among women in stable relationships (OR=0.56, 95% CI=0.45, 0.69) and those with a higher education level (OR=0.76, 95% CI=0.63, 0.93). Women who already knew that the HPV vaccine could be administered to adult women and boys showed a higher uptake (OR=1.22, 95% CI=1.00, 1.48 and OR=1.59, 95% CI=1.28, 1.97, respectively). Age and foreign-born status did not show an effect on vaccine uptake.

Regarding site characteristics, the invitation to participate by post resulted in lower HPV vaccine uptake than on-site face to face invitation (OR=0.13, 95% CI=0.02, 0.76). Sites with high vaccination program coverage of young girls also showed higher uptake (OR=3.23, 95% CI=0.95, 10.97). This became stronger (OR=4.57, 95% CI=1.33, 15.70) after the removal of German data. The addition of site-level characteristics into the model did not change the participant-level associations obtained but reduced the variance between sites (intraclass correlation).

Completion of 3 doses in vaccinated women (Table 2) was $\geq 85\%$ in all countries except in France (58%). Reasons for noncompliance among vaccinated women were loss to follow-up (n=108, 56.0%), personal decision to discontinue (n=53, 27.5%), pregnancy (n=19, 9.8%), availability-related reasons (e.g., lack of time and change of residence; n=10, 5.2%), and concurrent cancer

diagnosis (n=3, 1.6%). Of note, 6 women who became pregnant continued with vaccination after ceasing breastfeeding.

Predefined reasons for accepting or refusing vaccination (Appendix Text 1, available online) were collected for all sites except Sweden, where the only reasons for vaccine refusal were collected. A total of 2,522 acceptors and 658 refusers provided the reasons for their decision, whereas 26 (1%) and 240 (27%) did not reply.

The most cited reasons to accept vaccination (Figure 1A) were vaccine efficacy (85%–97%) and the seriousness of cervical cancer (89%–100%). Of note, only 49% and 55% of Danish and German women, respectively, chose vaccine safety as a reason to get vaccinated. Other reasons for vaccine acceptance mentioned by \geq 5 women were previous or current HPV infection or HPV-related conditions (n=13) and having relatives or friends with cervical or other cancers (n=10).

Reasons for refusing vaccination are provided for all countries combined owing to small numbers in some countries (Figure 1B). The most cited reason for refusing vaccination was safety concerns (country range=30% –59%). No reply was <15% in most countries except in Spain (23%), Sweden (37%), and Slovenia (43%). The need for more information was especially relevant in France (69%) and the UK (72%), although on the basis of low numbers (13 and 18 refusers, respectively). French (85%) and Belgian (27%) women needed to consult other people before being vaccinated.

Other reasons for vaccine refusal mentioned by ≥ 5 women were being in a stable relationship (n=9), previous or current HPV infection or HPV-related conditions (n=6), and needing more time to decide (n=6).

Of the 808, 495, and 848 participants vaccinated with the bivalent, quadrivalent, and nonavalent vaccine, respectively, 1,921 (89.3%) returned the safety card, with 649 reporting any adverse event, more than half of which were injection-site related (n=347). There were 2 serious adverse events, a sinus thrombosis and a skull fracture, neither was considered related to the vaccine.

DISCUSSION

In this multicenter study in Europe, the average acceptability of HPV vaccination among women attending cervical cancer screening was 75% (country range=50%—95%), and vaccine uptake among participants was 66.9% (country range=30%—92%).

The status of the adolescent public vaccination programs and the strategy used in this study to invite women for free HPV vaccination played a major role in vaccine uptake by adult women. Recruitment at healthcare service settings resulted in a high acceptance of

Table 2. Vaccine Acceptance, Uptake, and Completion Percentages by Country

Country	Number of study participants	Questionnaire vaccine acceptance, n (%)	Subjects with ≥1 dose administered, n (%)	Subjects with 3 doses administered, n (%)
Convenience				
Belgium	308	261 (84.7)	238 (77.3)	204 (66.2)
Finland	510	459 (90.0)	443 (86.9)	421 (82.6)
France	63	50 (79.4)	50 (79.4)	29 (46.0)
Germany	323	305 (94.4)	299 (92.6)	254 (78.6)
Slovenia	610	303 (49.8)	303 (49.7)	290 (47.5)
Spain	693	569 (82.1)	564 (81.4)	513 (74.0)
UK	434	416 (95.9)	NA ^a	NA ^a
Population based				
Denmark	347	191 (55.0)	145 (41.8)	141 (40.6)
Sweden	360	194 (53.9)	109 (30.3)	106 (29.4)
Total	3,648	2,748 (75.3)	2,151 (66.9) ^b	1,958 (60.9) ^b

^aNA because UK conducted a questionnaire-only study.

HPV vaccination (>80%) except in Slovenia (49.7%). However, acceptance by Slovenian sites (67% in Litija; 24% in Nova Gorica) reflects the variability in uptake already observed in different regions in Slovenia in the 2016–2017 young girls immunization program (46.4%, range=33.9%–78.3%).³⁰ This is consistent with results observed in Belgium, with high variability of vaccine uptake in study participants (98% in Ghent; 55% in Brussels), similar to the 90% and 35% uptake in young girls,²⁵ potentially related to a higher proportion of women from

low-income countries and with lower SES in Brussels. However, the high uptake in German adult women (93%) is not concordant with the low uptake (around 40%) at young ages in public programs.²⁹ An explanation could include being offered HPV vaccination face to face by the doctor providing routine screening services and the strong effect of their recommendation to get vaccinated.^{36,37}

Significant individual factors associated with HPV vaccine uptake included not being in a stable relationship, lower education level, and previous awareness of

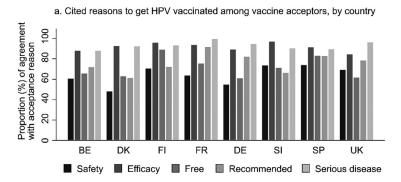
Table 3. Association of Individual and Contextual Factors With HPV Vaccine Uptake Using Multilevel Logistic Regression

Variable	Empty model	Model with individual characteristics, OR (95%CI)	Model with individual and site characteristics, OR (95%CI)	
Individual variables				
Stable relationship (yes versus no)	_	0.56 (0.45, 0.69)	0.56 (0.45, 0.69)	
Education level (above versus up to secondary education)	_	0.76 (0.62, 0.93)	0.76 (0.63, 0.93)	
Previous awareness of adult female vaccination (yes versus no)	_	1.22 (1.01, 1.48)	1.22 (1.00, 1.48)	
Previous awareness of male vaccination (yes versus no)	_	1.58 (1.28, 1.96)	1.59 (1.28, 1.97)	
Context variables				
Recruitment method (mail versus convenience)	_	_	0.13 (0.02, 0.76)	
Local HPV vaccination coverage in young girls (>70% vs <50%)	_	_	3.23 (0.95, 10.97)	
Model data				
ICC	40.5%	40.9%	29.7%	
AIC	3,296.1	3,128.9	3,125.4	

AIC, Akaike information criterion; HPV, human papillomavirus; ICC, intraclass correlation coefficient.

^bAmong 3,214 participating women excluding UK

NA, not applicable; UK, United Kingdom.



b. Cited reasons to refuse the HPV vaccine among vaccine refusers, all countries combined

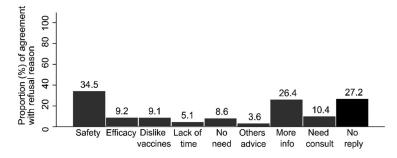


Figure 1. Provided reasons for vaccine (A) acceptance or (B) refusal.

Note: Countries legend: BE, DK, DE, FI, FR, SI, SP, and UK. Predefined acceptance reasons explored were *HPV* vaccine is safe, Vaccine protects against cervical cancer/genital warts (Efficacy), *HPV* vaccine is offered for free, It is recommended to get the *HPV* vaccine, and Cervical cancer is a serious disease. Predefined refusals reasons explored were I am concerned about *HPV* vaccine safety/side effects, I am concerned about whether the *HPV* vaccine works and how long it lasts (Efficacy), I do not like vaccines (Dislike vaccines), I do not have time (e.g., work's schedule, transportation issues,...) (Lack of time), I feel I might not benefit from the *HPV* vaccine protection (No need), I have been personally advised not to get vaccinated (Others advice), I need more information, I need to consult other people.

BE, Belgium; DE, Germany; DK, Denmark; FI, Finland; FR, France; HPV, human papillomavirus; SI, Slovenia; SP, Spain; UK, United Kingdom.

HPV vaccination indication for adult women or male individuals. In agreement with study findings, being single was also associated with higher acceptance in Sweden²¹ and Greece.²³ Swedish and German women²⁰ had also shown a higher acceptance at lower education level, but acceptance in Greece was lower in less educated women. Theories for vaccine refusal in more educated women include higher exposure to contradictory and possibly inaccurate information regarding the HPV vaccine. 38 In contrast to the observed lack of association for age, multivariate analyses showed lower HPV acceptance with increasing age in Germany and Greece probably because of their recruitment of women up to age 65 years. To the best of the authors' knowledge, no previous studies explored women's awareness of HPV vaccine eligibility of adult women.

The main reasons for vaccine uptake were trust in vaccine efficacy and perceived seriousness of cervical cancer, whereas safety concerns and the need for more information or consultation with other people were the most cited reasons for refusal. This is consistent with the qualitative findings in a European systematic review

where men and women of all ages were asked about HPV vaccine for adults and children.³⁹

Therefore, to achieve high acceptance rates of the HPV vaccine, irrespective of the targeted age groups of the programs, it is important to involve healthcare providers in the invitation and to address the potential disinformation and misinformation in the general population regarding vaccine safety and efficacy.

COHEAHR-WP4 is a study conducted in Europe, where there are occasional anti-vaccine movements (negative publicity), and the burden of cervical cancer and perceived risk is lower than in low-income countries. These study findings are consistent with preliminary results of a systematic review of HPV vaccine acceptability by middle-aged women that suggests very high and consistent acceptability in African and Latin American countries (80% average) and a higher variability in Asian populations (range by country=60%–80%). Africa and Latin America are regions with high incidence and mortality rates of cervical cancer.

Countries in Central and Eastern Europe and low-/middle-income countries, where HPV vaccination will be introduced shortly, are advised to explore strategies other than routine HPV vaccination of 1 or few adolescent cohorts. Extended age at vaccination could result in larger impacts in a shorter period on the basis of available scientific data. Furthermore, vaccination should significantly reduce costs associated with screening frequency and diagnostic and treatment procedures. 12

In settings where HPV testing is feasible, the HPV-FASTER strategy could tackle the limitations of cytology-based screening programs by using HPV testing as a screening tool, largely based on self-sampling procedures, and moving toward an improved once-in-a-lifetime screening and vaccination visit if current trials confirm the value of 1-dose vaccination also in middleaged women. 43,44 In populations where compliance with the follow-up of positive results is a major barrier, 1-visit interventions (HPV vaccination combined with HPV screen and treat) could be worth evaluating. 45 Furthermore, data are accumulating showing that vaccination of middle-aged women could potentially reduce transmission to their sexual partners⁴⁶ and boost herd protection.47 If these results can be replicated, the HPV-FASTER strategy could result in an additional reduction of HPV infections and their consequences.

Limitations

This study allowed for exploration of 2 of the HPV-FASTER strategy uncertainties: logistical challenges (how to best integrate vaccine administration in already established screening efforts) and societal challenges (whether HPV vaccination is an accepted cervical cancer prevention strategy when offered to adult women). However, the adaptations in the integration of vaccination into each regional or national screening services make the interpretation and representativeness of overall study findings somewhat challenging. The low response in countries where invitation was done by postal mail might reflect a lower acceptance among those who did not reply. By contrast, the convenience sampling in healthcare centers might over-represent women with higher concerns for their health and women interested in free HPV vaccination referred by friends or other study participants.

CONCLUSIONS

Within the limitations of the study size in each country, the results suggest that there are no major opinion barriers in the population to HPV vaccination of adult women in several countries in Europe. Acceptance and completion of the vaccination program are especially high when free vaccination is offered face to face by healthcare professionals and strongly dependent on the recruitment method used, coverage

achieved by national HPV vaccination public programs, and relationship status of women. There were no safety concerns in vaccinated women within the study; however, more information and safety reassurance to the public continue to be relevant for informed decision making.

ACKNOWLEDGMENTS

The authors would like to acknowledge the study contributions from Steven Weyers and Catherine Van Pachterbeke in Belgium; Katja Harjula, Kaisa Heikkilä, Mari Hokkanen, and Mervi Nummela in Finland; Prof. Olivier Graesslin, Dr. Jean-Paul Bory, Dr. Emilie Raimond, Dr. Philippe Benoit, Dr. Coralie Barbe, Mrs. Nathalie Rau, and Mrs. Florine Hardy in France; Jožefa Kežar and Lara Beseničar Pregelj in Slovenia; Marta Felez, Laura Monfil, Esther Roura, Carlos Amselem, Nuri Boadas, Mercé Lladó, Eva Barnés, Elisabeth Merino, Alexandra Bonmatí, and Mar Cadiñanos in Spain; Miriam Elfström, Angelica Lindén Hirschberg, and Berit Legerstam in Sweden; and Janet Austin, Lorna Sutcliffe, Lesley Ashdown-Barr, and Tony Hollingworth in the United Kingdom.

HPV vaccines used in the study were provided at no cost by GlaxoSmithKline Biologicals SA and Sanofi Pasteur Merck Sharp & Dohme (MSD), which had no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit for publication. GlaxoSmithKline Biologicals SA and Sanofi Pasteur MSD were provided the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for final content and interpretation.

This research was funded by the European Commission FP7 Framework Health 2013 Innovation 1 (Grant 603019; Comparing Health Services Interventions for the Prevention of HPV-Related Cancer project). This work was also partially supported in Spain by the Instituto de Salud Carlos III (Spanish Government), cofunded by FEDER funds/European Regional Development Fund—a way to build Europe (Redes temáticas de investigación cooperativa en salud RD12/0036/0056 [FXB, LB], Juan de la Cierva de Incorporacion IJCI-2016-29502 [CR], Centro de Investigación Biomédica en Red: Epidemiologia y Salud Pública CB06/02/0073 [SDS], Centro de Investigación Biomédica en Red: Oncologia CB16/12/00401 [LB, FXB]), and the Agència de Gestió d'Ajuts Universitaris i de Recerca (Catalan Government 2014SGR756 [SDS, CR], 2014SGR1077 [FXB, LB], 2017SGR793 [AA] and 2017SGR1718 [FXB, LB], and 2017SGR1085 [SDS]). The authors thank CERCA Programme/ Generalitat de Catalunya for institutional support at the Catalan Institute of Oncology.

Tasks completed by each author are as follows: study design (CR, MP, ML, JD, SKK, KUP, MA, JC, CC, SDS, and FXB); collection, analysis, and interpretation of data (all authors); draft manuscript writing (CR and FXB); and critical review, discussion, and approval of the final manuscript (all authors).

The following authors declare receiving research funding through their institution from GlaxoSmithKline Biologicals SA (CR, LB, ML, SDS, and FXB), MSD (CR, LB, ML, JD, CM, SKK, SDS, and FXB), or Sanofi Pasteur MSD (CR, LB, ML, MH, JD, SKK, KUP, SDS, and FXB); reimbursement of travel expenses for attending symposia, meeting, or conferences from GlaxoSmithKline Biologicals SA

(SDS and FXB), MSD (FXB), MSD (CC), or Sanofi Pasteur MSD (MTF, SDS, and FXB); or honorarium as a speaker or scientific advisory board member from GlaxoSmithKline Biologicals SA (KUP), MSD (SKK, JC, and FXB), MSD (CC), or Sanofi Pasteur MSD (SKK and FXB). No other financial disclosures were reported.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2020.08.032.

REFERENCES

- Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8(2):e191–e203. https://doi.org/10.1016/S2214-109X(19) 30482-6.
- Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J. Cervical cancer screening in Europe: quality assurance and organisation of programmes. Eur J Cancer. 2015;51(8):950–968. https://doi.org/10.1016/j. ejca.2015.03.008.
- Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis.* 2010;202(12):1789–1799. https://doi.org/10.1086/657321.
- Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials [published correction appears in *Lancet*. 2015;386(10002):1446]. *Lancet*. 2014;383(9916):524–532. https://doi.org/10.1016/S0140-6736(13)62218-7.
- Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer [published correction appears in *Vaccine*. 2013;31(52):6266]. *Vaccine*. 2012;30 (suppl 5):F88–F99. https://doi.org/10.1016/j.vaccine.2012.06.095.
- Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev. 2017(8):CD008587. https://doi.org/ 10.1002/14651858.CD008587.pub2.
- Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev.* 2018(5):CD009069. https://doi.org/10.1002/14651858.CD009069.pub3.
- Garland SM, Brotherton JML, Moscicki AB, et al. HPV vaccination of immunocompromised hosts. *Papillomavirus Res.* 2017;4:35–38. https://doi.org/10.1016/j.pvr.2017.06.002.
- Martínez-Gómez X, Curran A, Campins M, et al. Multidisciplinary, evidence-based consensus guidelines for human papillomavirus (HPV) vaccination in high-risk populations, Spain, 2016. Euro Surveill. 2019;24(7):1700857. https://doi.org/10.2807/1560-7917.ES.2019. 24.7.1700857.
- Basu P, Bhatla N, Ngoma T, Sankaranarayanan R. Less than 3 doses of the HPV vaccine: review of efficacy against virological and disease end points. *Hum Vaccin Immunother*. 2016;12(6):1394–1402. https://doi. org/10.1080/21645515.2016.1146429.
- Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis [published correction appears in *Lancet Glob Health*. 2017;5(7):e662]. *Lancet Glob Health*. 2016;4(7):e453–e463. https://doi.org/10.1016/S2214-109X(16)30099-7.
- Bosch FX, Robles C, Díaz M, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. *Nat Rev Clin Oncol*. 2016;13(2):119–132. https://doi.org/10.1038/nrclinonc.2015.146.

- Silverberg MJ, Leyden WA, Lam JO, et al. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a U.S. health-care setting: a population-based case-control study. *Lancet Child Adolesc Health*. 2018;2(10):707-714. https://doi.org/10.1016/ S2352-4642(18)30220-7.
- Cervarix. European Medicines Agency. https://www.ema.europa.eu/ medicines/human/EPAR/cervarix. Updated June 2019. Accessed August 10, 2020.
- Gardasil. European Medicines Agency. https://www.ema.europa.eu/medicines/human/EPAR/gardasil. Updated March 2020. Accessed August 10, 2020.
- Gardasil 9. European Medicines Agency. https://www.ema.europa.eu/ medicines/human/EPAR/gardasil-9. Updated May 2020. Accessed August 10, 2020.
- FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. U.S. Food and Drug Administration. October 5, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm. Accessed October 11, 2018.
- Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68(32):698–702. https://doi.org/10.15585/mmwr.mm6832a3.
- Donders GG, Gabrovska M, Bellen G, et al. Knowledge of cervix cancer, human papilloma virus (HPV) and HPV vaccination at the moment of introduction of the vaccine in women in Belgium. *Arch Gynecol Obstet*. 2008;277(4):291–298. https://doi.org/10.1007/s00404-007-0487-1.
- Kuitto K, Pickel S, Neumann H, Jahn D, Metelmann HR. Attitudinal and socio-structural determinants of cervical cancer screening and HPV vaccination uptake: a quantitative multivariate analysis. *J Public Health*. 2010;18(2):179–188. https://doi.org/10.1007/s10389-009-0308-z.
- Sundström K, Tran TN, Lundholm C, Young C, Sparén P, Dahlström LA. Acceptability of HPV vaccination among young adults aged 18-30 years—a population based survey in Sweden. *Vaccine*. 2010;28(47):7492–7500. https://doi.org/10.1016/j.vaccine.2010.09.007.
- Napoli C, Tafuri S, Chironna M, Quarto M, Da Molin G. Cervical cancer prevention and health inequalities: an ad-hoc survey in Italian women. *Public Health.* 2011;125(9):626–631. https://doi.org/10.1016/j.puhe.2011.05.009.
- Agorastos T, Chatzistamatiou K, Zafrakas M, et al. Distinct demographic factors influence the acceptance of vaccination against HPV [published correction appears in *Arch Gynecol Obstet*. 2015;292 (1):207]. *Arch Gynecol Obstet*. 2015;292(1):197–205. https://doi.org/10.1007/s00404-015-3614-4.
- Horn J, Denecke A, Luyten A, et al. Reduction of cervical cancer incidence within a primary HPV screening pilot project (WOLPHSCREEN) in Wolfsburg, Germany. Br J Cancer. 2019;120(10):1015–1022. https://doi.org/10.1038/s41416-019-0453-2.
- Vandermeulen C, Braeckman T, Roelants M, et al. Vaccinatiegraad in vlaanderen in 2016 [Vaccination coverage in 2016 in Flanders]. Flanders: Agency for Care and Health. https://www.zorg-en-gezondheid. be/sites/default/files/atoms/files/VIB%202017-2%20-%20Vaccinatiegraad%20in%20Vlaanderen%20in%202016.pdf. Published 2017. Accessed July 30, 2019.
- 26. Danish Health Authority, Danish Medicines Agency, Statens Serum Institut. Børnevaccinationsprogrammet Årsrapport [The childhood vaccination program annual report 2017]. København, Denmark: Danish Health Authority. https://www.ssi.dk/-/media/arkiv/dk/vaccination/boernevaccinationsprogrammet/boernevaccprogramaarsrap2017_23apr18.pdf?la=da. Published April 17, 2018. Accessed November 21, 2019.
- HPV-rokotuskattavuusraportit 2015 [HPV vaccination coverage reports 2015]. Finnish Department of Health and Welfare. http:// www.thl.fi/roko/rokotusrekisteri/hpvraportit2015/. Updated 2015. Accessed August 10, 2020.

- Données de couverture vaccinale papillomavirus humains (HPV) par groupe d'âge. Public Health France. https://www.santepubliquefrance. fr/determinants-de-sante/vaccination/articles/donnees-de-couverturevaccinale-papillomavirus-humains-hpv-par-groupe-d-age. Updated May 20, 2019. Accessed November 21, 2019.
- Rieck T, Feig M, Siedler A, Wichmann O. Aktuelles aus der KVimpfsurveillance –impfquoten ausgewählter schutzimpfungen in Deutschland [Coverage of selected vaccinations in Germany]. Berlin, Germany: Robert Koch Institut; Published January 4, 2018. https:// doi.org/10.17886/EpiBull-2018-001.3.
- Zaletel M, Vardic D, Hladnik M, eds. Zdravstveni Statistični Letopis 2016 [Health Statistics Report 2016]. Ljubljana, Slovenia: Nacionalni inštitut za javno zdravje. http://www.nijz.si/sl/publikacije/zdravstvenistatisticni-letopis-2016. Published 2018. Accessed December 11, 2018.
- Spanish Ministry of Health. Consumption and social welfare. [Vaccination coverage in Spain; 2017]. Madrid, Spain: Spanish Ministry of Health. https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/coberturas/docs/Todas_las_tablas2017.pdf. Published 2018. Accessed November 21, 2019.
- Swedish Public Health Authority. Statistics for HPV vaccinations proportion of vaccinated girls up to and including 2015-12-31. Solna, Sweden: Swedish Public Health Authority. https://www.folkhalsomyndigheten.se/globalassets/statistik-uppfoljning/vaccinationsstatistik/hpv/statistik-for-hpv-vaccinationer-andel-vaccinerade-flickor-tom-2015-12-31.pdf. Published December 31, 2015. Accessed November 21, 2019.
- Public Health England. Human papillomavirus (HPV) vaccination coverage in adolescent females in England: 2017/18 report for England. London, United Kingdom: Public Health England. https://assets. publishing.service.gov.uk/government/uploads/system/uploads/ attachment_data/file/760902/HPV_2017_2018_annual_report.pdf. Published December 2018. Accessed November 21, 2019.
- Austin PC, Merlo J. Intermediate and advanced topics in multilevel logistic regression analysis. Stat Med. 2017;36(20):3257–3277. https://doi.org/10.1002/sim.7336.
- Goldstein H, Browne W, Rasbash J. Partitioning variation in multilevel models. *Underst Stat.* 2002;1(4):223–231. https://doi.org/ 10.1207/S15328031US0104_02.
- Reiter PL, Bustamante G, McRee AL. HPV vaccine coverage and acceptability among a national sample of sexual minority women ages 18-45. Vaccine. 2020;38(32):4956-4963. https://doi.org/10.1016/j. vaccine.2020.06.001.
- Wang LD, Lam WW, Fielding R. Cervical cancer prevention practices through screening and vaccination: a cross-sectional study among Hong Kong Chinese women. *Gynecol Oncol.* 2015;138(2):311–316. https://doi.org/10.1016/j.ygyno.2015.05.018.

- Patel PR, Berenson AB. Sources of HPV vaccine hesitancy in parents. Hum Vaccin Immunother. 2013;9(12):2649–2653. https://doi.org/ 10.4161/hv.26224.
- Karafillakis E, Simas C, Jarrett C, et al. HPV vaccination in a context of public mistrust and uncertainty: a systematic literature review of determinants of HPV vaccine hesitancy in Europe. *Hum Vaccin Immunother*. 2019;15(7–8):1615–1627. https://doi.org/10.1080/ 21645515.2018.1564436.
- 40. Robles C, Bruni L, De Sanjose S, and Bosch FX, Systematic review on HPV vaccine acceptability among women above age 25. Paper presented at: HPV 2015: 30th International Papillomavirus Conference & Clinical and Public Health Workshops; September 17-21, 2015; Lisbon, Portugal. https://www.hpv2015.org/. Accessed January 23, 2018.
- Drolet M, Bénard É, Pérez N, Brisson M, HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lan*cet. 2019;394(10197):497–509. https://doi.org/10.1016/S0140-6736 (19)30298-3.
- 42. Simms KT, Steinberg J, Caruana M, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. *Lancet Oncol.* 2019;20(3):394–407. https://doi.org/10.1016/S1470-2045(18)30836-2.
- Salmerón J, Torres-Ibarra L, Bosch FX, et al. HPV vaccination impact on a cervical cancer screening program: methods of the FASTER-Tlalpan Study in Mexico. Salud Publica Mex. 2016;58(2):211–219. https:// doi.org/10.21149/spm.v58i2.7790.
- Effectiveness of HPV vaccine in Thai adult women. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03763565. Updated December 4, 2018. Accessed July 18, 2020.
- Kuhn L, Denny L. The time is now to implement HPV testing for primary screening in low resource settings. *Prev Med.* 2017;98:42–44. https://doi.org/10.1016/j.ypmed.2016.12.030.
- Wissing MD, Burchell AN, El-Zein M, Tellier PP, Coutlée F, Franco EL. Vaccination of young women decreases human papillomavirus transmission in heterosexual couples: findings from the HITCH Cohort Study. Cancer Epidemiol Biomarkers Prev. 2019;28(11):1825–1834. https://doi.org/10.1158/1055-9965.EPI-19-0618
- Tabrizi SN, Brotherton JML, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis.* 2014;14(10):958–966. https://doi.org/10.1016/S1473-3099 (14)70841-2.