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Association between human papillomavirus vaccine uptake and cervical cancer screening in the Netherlands: Implications for future impact on prevention

Anneke Steens[1], Cornelia C.H. Wielders[1,2], Johannes A. Bogaards[1,3], Hendriek C. Boshuizen[4], Sabine C. de Greeff[1] and Hester E. de Melker[1]

[1] Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[2] Pallas Health Research and Consultancy B.V., Rotterdam, The Netherlands
[3] Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, The Netherlands
[4] Expertise Centre for Methodology and Information Services, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Several countries recently added human papillomavirus (HPV) vaccination to cervical cancer screening in the effort to prevent cervical cancer. They include the Netherlands, where both programs are free. To estimate their combined future impact on cancer prevention, information is needed on the association between participation in vaccination now and in screening in the future and on what groups are at risk for nonparticipation. We studied the association between participation in screening by mothers and in vaccination by their daughters. Girls' vaccination status was matched by house-address with their mothers' screening participation. We estimated the effect on cancer incidence by means of computer simulation. We investigated risk groups for nonparticipation using multivariable multilevel logistic regression and calculated population-attributable fractions. Our results, based on 89% of girls invited for vaccination in 2009 (n = 337,368), show that vaccination status was significantly associated with mothers' screening participation (odds ratio: 1.54 [95% confidence interval: 1.51–1.57]). If a mother's screening is taken as proxy of a girl's future screening, only 13% of the girls will not participate in either program compared to 23% if screening alone is available. The positive association between vaccination and screening resulted in slightly lower model estimates of the impact of vaccination on cancer incidence, compared to estimates assuming no association. Girls with nonwestern ethnicities, with young mothers, who live in urban areas with low socioeconomic status, are at risk for nonparticipation. A significant part of potential nonscreeners may be reached through HPV vaccination. Estimates made before vaccination was introduced only slightly overestimated its impact on cervical cancer incidence.

Cytology-based screening of women for cervical cancer effectively reduces its morbidity and mortality. Further reduction is anticipated in the coming decades owing to the recent addition of human papillomavirus (HPV) vaccination to prevention efforts.[1] Cervical screening has long been established in most western countries. In the Netherlands, about 77% of eligible women (aged 30–60 years) are screened.[2] Now, more than half of the cervical cancers occur in women who do not participate in screening (overall incidence: 4.9–5.9 per 100,000 women).[3,4] An increasing number of countries has added an HPV vaccination program to an ongoing cervical cancer screening program. Since 2009, a bivalent HPV vaccine[5] is included in the Dutch National Immunization Program (NIP), targeting 12-year-old girls. In March 2009, a catch-up campaign was organized for girls who were 13–16 years old in that year.

The bivalent vaccine covers only HPV serotypes 16 and 18, which cause about 70% of all cervical cancer cases.[6] As the vaccine does not give full protection against HPV infection,[7,8] cervical screening of all women remains important. However, the future screening behavior of vaccinated *versus* nonvaccinated girls will not be known for more than a decade. In the interim, insight into screening behavior is essential input for mathematical models aiming to predict the future impact of the combined cervical cancer prevention efforts. In particular, such insight may reveal whether the

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Abbreviations: CBS: Statistics Netherlands; CIS: Cervix Information System—database for cervical screening; GP: General practitioner; HPV: human papillomavirus; NIP: National Immunization Program; OR: odds ratio; P_e: probability of nonparticipation for the risk group; P_u: probability of nonparticipation for the reference group; P_v: probability of screening for vaccinated girls; P_{uv}: probability of screening for nonvaccinated girls; PAF: population-attributable fraction; SCP: Dutch Institute for Social Research; SES: socioeconomic status

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Correspondence to: Hester E. de Melker, National Institute for Public Health and the Environment (RIVM), Centre for Infectious Disease Control, P.O. Box 1, 3720 BA Bilthoven, The Netherlands, Tel.: +31-30-247-3958, Fax: +31-30-274-4409, E-mail: hester.de.melker@rivm.nl

What's new?

The study estimates the association between the vaccination status of teenage girls against the human papillomavirus and the participation of their mothers in cervical cancer screening using nationwide registries. The authors also quantify the projected impact of the positive association between girls' HPV vaccination and their own screening later in life on the future incidence of cervical cancer. Finally, they identify groups at risk for non-participation in cancer prevention with the view to assist the design of future interventions. There is concern that the same women who did not receive the vaccine against the human papillomavirus as teenagers will also not participate in cervical cancer screening as adults. The authors show that participation is indeed selective, but that the two cervical cancer prevention programs are nonetheless set to complement each other, ensuring the cost-effectiveness of HPV vaccination.

two programs are complementary or whether the same individuals will participate in both, whereas others are missed by both.

Social literature indicates that a mother's attitudes are positive predictors of her children's attitudes in adulthood.[9,10] Thus, a mother's screening is perhaps the best available proxy for a daughter's future screening. Moreover, studies in the United States and Belgium suggest that a mother's participation in cervical screening was positively associated with a girl's likelihood of vaccination.[11,12] Until now, studies modeling the impact of vaccination added to cervical screening have ignored the possibility that screening participation would be lower among unvaccinated girls.[1,13,14] If girls who do not obtain vaccination are the same ones who will later not be screened, this selective uptake could diminish the impact of the prevention program, making vaccination less cost-effective.[15–18]

The overall effectiveness of cervical cancer prevention depends on participation of the targeted women. Despite the identification of risk groups for nonparticipation in each of the two programs, [12,19,20] it is not yet known which groups are likely to be missed by both. Insight into future screening participation of adolescent girls, and its determinants, can facilitate design of interventions to reach potential nonparticipants.

In our study, we investigated the association between participation in vaccination and participation in screening, using a mother's screening as proxy for a girl's future screening. We determined the extent to which model-based estimates of the effectiveness of cervical cancer prevention depend on the possible association between vaccination and screening participation. Furthermore, we identified which background characteristics are associated with nonparticipation in the two prevention programs, and determined the population-attributable fractions (PAFs) of the variables on nonparticipation. The PAF helps to determine on which risk groups interventions should be focused to maximally increase participation, as it takes into account the size of the risk group in the general population as well as the strength of the association with the outcome (*i.e.*, participation).

Methods

HPV vaccination campaign and cervical cancer screening in the Netherlands

The HPV vaccination campaign was co-ordinated by the National Institute for Public Health and the Environment (RIVM). Municipal health services were in charge of local implementation. Medical professionals were informed by newsletter, meetings and a dedicated website. Eligible girls received a personal invitation letter with an informational leaflet.[21] For the general public, a website offered further information that could be downloaded in various languages. Girls were invited to visit local sessions for free vaccination. Such sessions have been organized previously for meningococcal vaccination and are also used for routine childhood vaccination.

The cervical screening program is carried out by general practitioners (GPs), as virtually everybody has a GP in the Netherlands. The program includes seven cytology-based screening rounds at 5-year intervals starting at the age of 30 years. Each woman receives a personal invitation to make an appointment with her GP for each round of screening. The screening is provided for free.

Study design and data collection

Data on all girls invited for the HPV catch-up campaign in 2009 (birth cohorts, 1993–1996) were extracted from Praeventis, the Dutch vaccination registry based at the RIVM.[21] For each girl, the complete home-address, year and country of birth, country of birth of both parents (if available), and, if the girl was vaccinated, the date, location and brand-name of HPV vaccination were obtained.

Data on cervical cancer screening participation in 2005–2010 are kept by the Cervix Information System (CIS) from which home-address, year of birth, date of invitation for screening and date of screening (if the woman participated in screening) were extracted. For technical reasons, data on one province (Limburg; 6.8% of Dutch inhabitants[22]) were not obtained.

Consultation with advisors on ethical clearance and the Dutch law for data privacy (WBP) revealed that, as our data were anonymous to the researchers, clearance and informed consent were not necessary.

After a strict protocol, a trusted third party (not otherwise involved in our study) matched the girls with mothers based on their shared home-address: street and number, city and a six-digit postal code having four numerals and two letters. The code identifies each residence in the country, with numbers indicating municipality and neighborhood and letters indicating the street. To perform the matching, four files were created. Based on the vaccination registry, file I contained the address of all eligible girls and file II contained

their vaccination history. File I was sent to CIS, where data were extracted on all women whose addresses matched those of the girls. The women's addresses were stored in file III and their screening data were stored in file IV. In all the files, the girls and women had individual identification numbers. The third party used the four files to match girls and women by using identification numbers and address, and then securely stored the files. For each girl, instead of the full address, the researchers received only the four numerals of the postal code, indicating the neighborhood. Additional information at the aggregate level (Table 1) was derived from the websites of Statistics Netherlands (CBS, http://statline.cbs.nl/statweb/) and the Dutch Institute for Social Research (SCP, www.scp.nl) and was linked to the matched Praeventis–CIS database using postal code or municipal code, whichever was applicable.

We included data from Praeventis and CIS up to December 31, 2010. We excluded from analysis all girls for whom no mother or multiple mothers were identified, who left the Netherlands or died before the start of the vaccination campaign (January 1, 2009), who moved to the Netherlands after January 1, 2009 or who did not fit the eligibility criteria (birth cohorts, 1993–1996). Furthermore, we excluded girls who appeared to have more than three sisters. In such cases, we assumed false matching, as a mother is unlikely to have four daughters born in the years 1993 through 1996.

Data analyses

In an ecological design, data from different sources and at different levels of aggregation were combined with vaccination data on girls and screening data on the mother (Table 1). The main variables were completion of the HPV vaccination regimen (with at least three HPV vaccinations) and participation in cervical screening (with at least one date of screening). Screening participation of the mother was used as proxy for the girl's future screening participation. Using + and – signs for yes and no, we created a combined categorical variable with four levels (++/− +/+ −/− −) representing girls' completion of the vaccination program (yes or no) and her projected future screening. Information on degree of urbanization, socioeconomic status (SES) and the proportion of votes for Christian political parties during the last House of Representatives elections (2010) were available on aggregate level. The political variable was used because very conservative Protestants in the Netherlands (*e.g.*, members of the Dutch Reform Church) tend to refuse vaccination for religious reasons. These Protestants are socio-geographically clustered[23] and comprise the majority who vote for Christian political parties.[24,25] The proportion of votes for such parties served as proxy for avoidance of vaccination based on religious beliefs. The variable will henceforth be termed "Christian conservativeness."

Descriptive analyses were performed in which we ignored the hierarchy of the data, as mothers can have more than one daughter (as did 29,669 of our sample) and girls are clustered within neighborhoods (n = 3,734) and municipalities (n = 404). Analyses were performed in SAS 9.2 (SAS Institute, Cary, NC).

Multilevel logistic regression analysis

To address the hierarchy of data, we performed multilevel multivariable logistic regression analysis[26] (SAS, glimmix procedure), including a random intercept for each level of aggregation (neighborhood, municipal). Such a model handles outcomes as a function of determinants that are available at different levels and corrects for the effect of clustering. Beyond the individual level, determinants become group level determinants.

We investigated the association between the girl's vaccination status and her future screening participation as odds ratio (OR), adjusting for her year of birth (individual level), ethnicity (individual level), her mother's age at delivery (individual level), SES (neighborhood level) and Christian conservativeness (municipal level). Degree of urbanization (neighborhood level) did not significantly confound the association and was therefore not included in the analysis.

Consequences for model-based studies

The effect of the association between participation in the vaccination and screening programs on cumulative (life-time) cervical cancer incidence was evaluated by computer simulation. The same simulation model was previously used to estimate the cost-effectiveness of HPV vaccination and the long-term impact of HPV vaccination in a population partially screened for cervical cancer.[1,15] Briefly, calculations were based on an individual-based model of cervical carcinogenesis, in which the natural history of cervical cancer was described as a consequence of persistent infection with any of the 14 oncogenic HPV types. The main data source for the model was a population-based screening trial, in which genotyping was performed on all samples positive for these high-risk HPV types.[27,28] The risk of being infected by these types was determined using a type-specific HPV transmission model[29] that was fitted to population-based prevalence data collected before introduction of the vaccine in the Netherlands.[30] Model fitting procedures and best-fitting parameters are described in the supplementary annexes of the previous publications.[1,29] Model estimates were determined by simulating the health trajectories of 100,000 girls, of whom 53% completed the vaccination regimen at the age of 12 years (first Dutch NIP cohort). We ignored the indirect effect (*i.e.*, herd immunity) and assumed full efficacy of the vaccine in preventing HPV-16/18 infection.

Cervical screening in the individual-based model was incorporated according to current Dutch screening guidelines. Heterogeneity in cervical screening participation was modeled with two parameters: (*i*) the probability that a woman is inclined to participate in screening sometime in her life (henceforth termed the life-time screening probability) and, if she does, (*ii*) the probability that she will undergo screening in a particular round (henceforth termed the per-round screening probability). We assumed a life-time screening

Table 1. Data source and year, level of aggregation, details of the data and variable definitions

Variable	Source	Year	Details	Defined variable
Individual level				
Birth cohort (girl)	Praeventis	2010	Year of birth	
Birth cohort (mother)	CIS	2010	Year of birth	*Mother's age at delivery of her daughter*: calculated by subtracting the mother's birth year from the birth year of her daughter. Categorized as <20 years, 20–24 years, 25–36 years, 37–40 years and >40 years. Note that the parity is unknown
HPV vaccination status	Praeventis	2010	Date and place of vaccination of the first, second and third dose	*Initiation of HPV vaccination*: having received at least one HPV vaccination
				Completion of HPV vaccination: having received at least three HPV vaccinations
Cervical screening participation	CIS	2005–2010	Date of participation of invited women between 2005 and 2010	*Screening participation*: a binary variable in which mothers with at least one date of screening were categorized as having participated in screening
Ethnicity	Praeventis	2010	Based on parents' country of birth. For administrative reasons, available only for girls who moved within or to the Netherlands after 2003 (29% of the girls)	Categorized as Dutch, migrants from western countries, Moroccan, Turkish, Surinamese, Netherlands Antillean/Aruban, migrants from other nonwestern countries and data missing
Neighborhood level (four numbers of postal code)				
Degree of urbanization	CBS	2010	Based on the density of addresses in the neighborhood (km^2)	Categorized as "very high" (>2,500 addresses per km^2); "high" (1,500–2,500), "moderate" (1,000–1,500), "low" (500–1,000) or "none" (<500)
Socioeconomic status (SES)	SCP	2006	Combination of the average income per household, the percentage of households with low income, no paid job and low average education	Five SES categories were defined: high SES, moderate–high SES, moderate–low SES, low SES and data missing (1.1%)[25,50]
Proportion of ethnic groups	SCP	2006	The proportion of people in a four-numeral postal code area that are Dutch, western migrants, Moroccan, Turkish, Surinamese, Netherlands Antillean/Aruban and migrants from other nonwestern countries	Note that the proportion of each ethnic group in a neighborhood was used only to check whether the lack of ethnicity data at the individual level was selective for some areas or groups
Municipality level				
Avoidance of vaccination based on religious beliefs (Christian conservativeness)	CBS	2010	Proportion of votes for 11 Dutch political parties during the last House of Representatives elections	The proportion of votes for the Christian political parties (Christian Union and the Reformed political party [SGP]) were taken together and categorized as 0–4, 5–14, 15–24 and ≥25%

Praeventis: the national vaccination registry; CIS: Cervix Information System (database with information on screening participation); CBS: Statline, Statistics Netherlands; SCP: Institute for Social Research; SGP: Reformed political party.

Table 2. Characteristics of sample, percentage of girls initiating and completing vaccination, percentage of the mothers participating in screening and combined participation in the two programs, presented for the different categories[1]

Variable	Category	Number (% of total)	% of girls who initiated vaccination	% of girls completing vaccination	% participating in screening	Combined participation (%)			
						+ Vaccination + screening	− Vaccination + screening	+ Vaccination − screening	− Vaccination − screening
Overall		337,368	58	53	77	43	34	10	13
Complete HPV vaccination regimen[2]	Yes	178,505 (53)	100	100	81	74	5.4	18	2.9
	No	158,863 (47)	10	0	72	NA	73	NA	27
Screening participation	Yes	258,291 (77)	60	56	100	56	44	NA	NA
	No	79,077 (23)	51	44	0	NA	NA	44	56
Birth cohort (girl)	1993 [ref]	84,843 (25)	55	50	76	40	36	10	14
	1994	85,800 (25)	58	53	77	43	34	10	13
	1995	83,516 (25)	59	54	77	44	33	11	13
	1996	83,209 (25)	59	55	77	44	33	11	13
Mother's age at delivery of her daughter	<20 Years	5,858 (1.7)	50	40	55	23	32	16	29
	20–24 Years	34,443 (10)	49	41	65	29	36	12	23
	25–36 Years [ref]	270,183 (80)	59	55	79	45	34	10	11
	37–40 Years	22,263 (6.6)	57	53	75	42	33	11	14
	>40 Years	4,621 (1.4)	51	45	66	32	34	13	21
Ethnicity[3]	Dutch [ref]	69,636 (21; 71[4])	59	55	79	45	34	10	11
	Other western country	6,430 (1.9; 6.5[4])	58	51	62	36	31	15	18
	Moroccan	4,414 (1.3; 4.5[4])	30	21	53	13	40	8	39
	Turkish	4,561 (1.4; 4.6[4])	43	33	64	23	41	10	25
	Suriname	3,766 (1.1; 3.8[4])	52	42	62	29	33	13	25
	Netherlands Antillean/ Aruban	1,439 (0.43; 1.5[4])	52	40	57	27	31	13	29
	Other nonwestern country	8,050 (2.4; 8.2[4])	56	45	62	31	31	15	23
	Data missing	239,072 (71)	58	54	78	44	34	10	12
Degree of urbanization	Low [ref]	126,491 (37)	57	53	80	44	36	9	11
	Middle low	53,211 (16)	60	56	79	46	33	10	11
	Moderate	47,062 (14)	58	53	77	43	34	10	13
	Middle high	40,296 (12)	59	54	74	42	32	11	14
	High	70,308 (21)	57	50	69	38	31	12	18

Table 2. Characteristics of sample, percentage of girls initiating and completing vaccination, percentage of the mothers participating in screening and combined participation in the two programs, presented for the different categories[1] (Continued)

Variable	Category	Number (% of total)	% of girls who initiated vaccination	% of girls completing vaccination	% participating in screening	Combined participation (%)			
						+ Vaccination + screening	− Vaccination + screening	+ Vaccination − screening	− Vaccination − screening
Socioeconomic status (SES)	High SES [ref]	38,186 (11)	63	59	78	47	31	11	11
	Moderate–high SES	138,596 (41)	59	55	80	45	34	9	11
	Moderate–low SES	107,738 (32)	57	52	77	42	35	10	13
	Low SES	49,128 (15)	53	46	66	33	33	12	21
	Data missing	3,720 (1.1)	58	53	72	41	31	11	16
Christian conservativeness	0–4% [ref]	237,846 (71)	60	55	76	44	32	11	13
	5–14%	72,279 (21)	57	52	77	42	35	10	12
	15–24%	13,219 (3.9)	43	40	78	33	45	7	15
	≥25%	14,024 (4.2)	31	28	76	23	53	5	19

[1]Combined participation represents girl's completion of the vaccination program (yes + or no −) and her assigned mother's participation in screening. NA: not applicable. [ref]: reference group for the calculation of PAFs. [2]Note that girls who start HPV vaccination but do not complete the regimen end up in the − + or − − categories. [3]For comparison: the distribution of ethnicity in the Netherlands among girls aged 13–16 years at January 1, 2009, was Dutch 78%, other western ethnicity 6.5%, Moroccan 3.1%, Turkish 3.6%, Suriname 2.6%, Netherlands Antillean/Aruban 1.2% and migrants from other nonwestern countries 4.9%.[22] [5]The first number is the percentage of the included population; the second is the percentage of that population with known ethnicity, as an indication of the percentage of the Dutch population.

probability of 90% and a per-round screening probability of 80% (Dutch scenario).[1] From the reported OR of the association between a girl's vaccination status and her mother's screening participation, we calculated either altered life-time screening probabilities or altered per-round screening probabilities for girls vaccinated (P_v) and unvaccinated (P_{uv}), using the standard formula: $OR = [1/(1 - P_v)]/[1/(1 - P_{uv})]$. We performed sensitivity analyses to explore the effect of the association under conditions of a lower screening coverage or a higher vaccination coverage. We changed the life-time screening probability to 50% and the per-round screening probability to 70% and kept the initial vaccination coverage; or we changed the vaccination coverage to 80% and kept the initial screening probabilities. Estimates were compared to the base-case assuming random participation (*i.e.*, similar screening probabilities for vaccinees and nonvaccines; OR: 1.0).

Population-attributable fraction

The PAF is an estimate of the percentage of nonparticipation in the prevention programs that can be attributed to each risk factor under study. We calculated (*i*) the PAF on nonparticipation in both programs and (*ii*) the PAF on participation in none or only one prevention program. We therefore defined a binary variable with outcome = 0 for (*i*) nonparticipation in both programs (− −) or (*ii*) participation in none or only one (− −/− +/+ −) and outcome = 1 for (*i*) participation in either program (− +/+ −/++) or (*ii*) participation in both programs (++).

The PAFs were determined as the change in probability of nonparticipation (outcome = 0) predicted by the model when the risk factor level was changed from the original value (P_e) to the reference value (P_u) using the formula: $100(P_e - P_u)/P_e$.[31] Table 2 summarizes reference groups. The probabilities were determined by fitting the multivariable multilevel logistic regression model (including girl's year of birth, ethnicity, mother's age at delivery, SES, degree of urbanization and religion), using maximum likelihood with Laplace approximation. We adjusted for clustering at the neighborhood and municipal level. The 95% confidence intervals (95% CI) around the PAF were based on the variability in the estimated probability of nonparticipation and determined using the method of Greenland and Drescher.[32] As our study included nearly all targeted girls in the Netherlands, the occurrence of the risk factor in the population was assumed to be known precisely (without error). In estimating the PAF for different ethnic groups, we excluded girls for whom ethnicity data were missing.

Results

Data characteristics

A total of 337,368 girls (89% of the initial data set, aged 13–16 years) matched to 306,789 mothers (aged 12–51 years at delivery of the girl) were included in the analysis (data flow, Fig. 1). Excluded girls (n = 39,934) did not differ from included girls regarding year of birth and the degree of urbanization or Christian conservativeness of their neighborhood, although their vaccination coverage was lower (initiation: 37%, completion: 26%) compared to girls included in the analysis (initiation: 58%, completion: 53%). Furthermore,

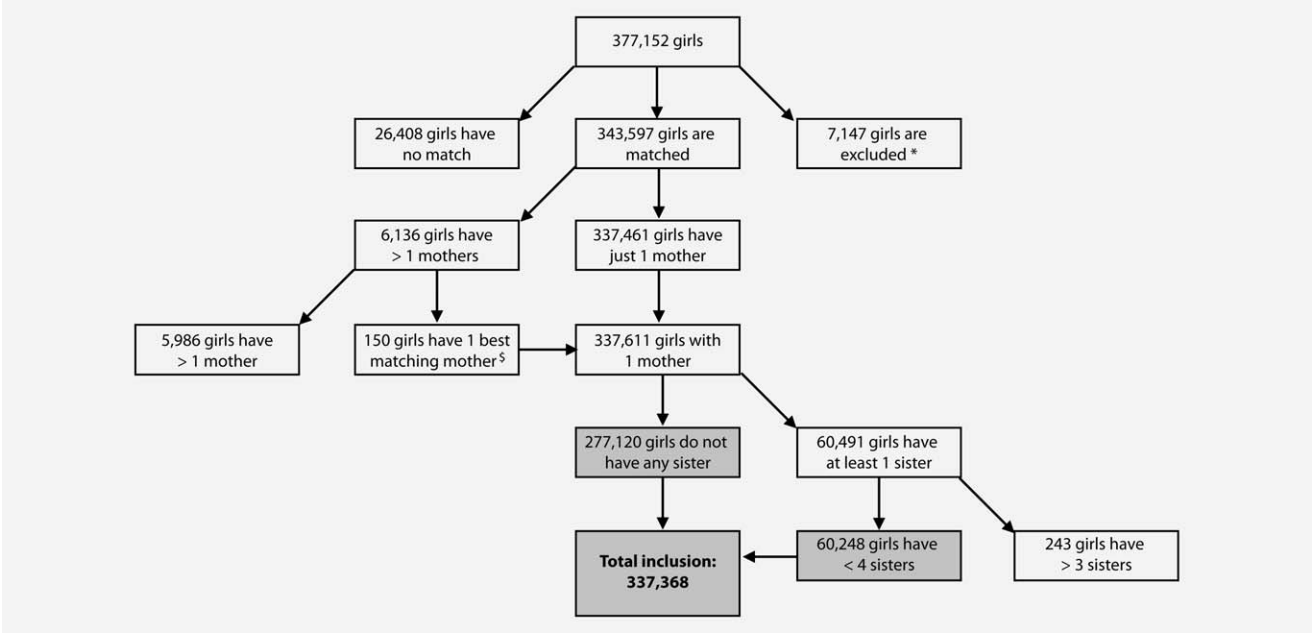

Figure 1. Data flow chart. The gray squares represent the included data. *Girls who left the Netherlands or died before the start of the vaccination campaign (January 1, 2009), who moved into the Netherlands after January 1, 2009 or who did not fit the eligibility criteria (birth cohorts 1993–1996) were excluded. $Girls and mothers were ideally matched on full address, which includes five items. In some cases, fewer than five items were available. If multiple mothers were identified for a girl, we included the one matched on the most items.

excluded girls had less often a Dutch ethnicity (14 *versus* 21%) and were living in neighborhoods with a lower SES (median: moderate–low *versus* moderate–high) than included girls. Ethnicity was unknown for 71% of the included girls, but the lack of these data was not associated with the HPV vaccination coverage, screening participation, the percentage of different ethnic groups in the neighborhoods or to the Christian conservativeness of the municipality. Girls with unknown ethnicity were slightly younger, and lived in more rural areas with slightly higher SES.

The association between vaccination and screening participation and its effect on model-based estimates of the impact of vaccination on future cancer incidence

Table 2 summarizes the distribution of vaccination and screening participation according to different characteristics of interest. The percentage of girls initiating vaccination was 58% and 53% completed the regimen. Of the mothers, 77% were screened at least once during 2005–2010. A girl's vaccination status was positively associated with her mother's screening participation (crude OR: 1.60 [95% CI: 1.57–1.62], adjusted OR: 1.54 [95% CI: 1.51–1.57]). Mothers of girls who completed the regimen participated more often in screening (81%) than mothers of unvaccinated girls (72%), and daughters of screened mothers more often completed the regimen (56%) than daughters of nonscreened mothers (44%). The association between *initiation* of the HPV vaccination regimen and screening participation was slightly less strong (crude OR: 1.44 [95% CI: 1.42–1.47], adjusted OR: 1.40 [95% CI: 1.38–1.43]) than the association between completion of the regimen and screening participation.

From the association between completion of HPV vaccination and participation in screening (OR: 1.54), we projected a life-time screening probability of 92% for vaccinated girls and 88% for unvaccinated girls (compared to 90% in case of random participation). Simulations based on these probabilities resulted in a slightly higher cumulative cervical cancer incidence than simulations that assumed random participation (Table 3). We estimated that in a cohort of 100,000 girls aged 12 years, the cumulative incidence of cervical cancer in the presence of screening but in the absence of vaccination would be 532 cases. At vaccination coverage of 53%, the incidence dropped to 338 cervical cancer cases in case of random participation in the prevention programs (36% reduction). Taking the association between vaccination and screening participation into account resulted in an incidence of 352 cases, a 34% reduction. Thus, the effectiveness of the vaccination program was only slightly overestimated if the association with screening was ignored. The effectiveness of HPV vaccination in this cohort was 35% if the association between vaccination and screening was projected onto per-round screening probabilities instead of life-time screening probabilities (data not shown).

The impact of the association between vaccination and screening participation on the relative effectiveness of the vaccination program was independent of the vaccination or screening coverage. Decreasing the life-time probability of screening from 90 to 50% and the per-round probability from 80 to 70% resulted in a cancer reduction of 37% if the association was ignored, and a 34% reduction if it was included in the model. Although the percentage is similar,

Table 3. Consequences of the association between completion of the vaccination regimen and future participation in screening on model-based estimates of the impact of HPV vaccination on the cumulative (life-time) cervical cancer incidence[1]

Screening probability					
P_v (%)	P_{uv} (%)	OR	Prevention programs in place	Cumulative incidence (per 100,000 girls)	Effectiveness of the vaccination program
Dutch scenario—vaccination coverage 53%					
90	*90.0*	NA	Screening; no vaccination	532	NA
90	*90.0*	1.00	Screening + vaccination	338	36%
91.8	*87.9*	1.54	Screening + vaccination	352	34%
Sensitivity analysis—decreased screening coverage					
50	*50.0*	NA	Screening; no vaccination	1,459	NA
50	*50.0*	1.00	Screening + vaccination	921	37%
55.0	44.3	1.54	Screening + vaccination	961	34%
Sensitivity analysis—increased vaccination coverage					
90	*90.0*	NA	Screening; no vaccination	532	NA
90	*90.0*	1.00	Screening + vaccination	239	55%
90.9	*86.6*	1.54	Screening + vaccination	253	52%

[1]Model estimates were derived for a cohort of 100,000 girls, of whom 53% are vaccinated at 12 years and 90% participate at least once in life-time in screening (Dutch scenario). We assumed no indirect effect of vaccination (*i.e.*, herd immunity) and full efficacy of completion of the HPV vaccination program in preventing HPV-16/18 infection.[1] We applied the OR as the association between completion of the vaccination regimen and participation in screening at least once in a life-time. Sensitivity analyses were performed using a decreased screening probability (50%) or an increased vaccination coverage (80%).
NA: not applicable; P_v = probability of screening among vaccinated girls; P_{uv} = probability of screening among nonvaccinated girls.

note that the absolute difference in prevented cervical cancer cases was larger (40 cases compared to 14 cases) at lower screening coverage. This is the result of the higher cumulative incidence (1,459 cases) in the absence of vaccination. Given a vaccination uptake of 80%, the effect on the model of including the association between vaccination and screening participation in the model still resulted in a 2.6% decrease of the effectiveness of vaccination, just as in the two preceding scenarios. Inherent to the increased vaccination coverage, the overall effectiveness of the vaccination program was larger: if 80% of girls were vaccinated, a reduction of 55 or 52% of the cervical cancer cases (assuming random participation or selective participation [OR: 1.54]) could be reached.

Determinants of (non)participation in prevention programs and its PAFs

The expected participation of the girl in the two prevention programs was associated with her mother's age at delivery, her ethnicity, degree of urbanization, SES and Christian conservativeness (Table 2). Girls unlikely to participate in any prevention program (− −) had mothers who were comparatively young or old at delivery (<25 years or >40 years; average age of delivery in the Netherlands = 31 years).[33] Their ethnicity reflected roots in Morocco (or to a lower extend, the Netherlands Antilles/Aruba, Turkey or Suriname); they lived in urban areas, with low SES or lived in a Christian conservative municipality. Interestingly, while a negative association was observed between the vaccination coverage and the Christian conservativeness, participation in screening did not depend on Christian conservativeness. Although vaccination coverage appears to be independent of the degree of urbanization, screening behavior was influenced by it.

The variables that contributed most to nonparticipation in both prevention programs (− −; Fig. 2*a*) were living in an area with low or moderate–low SES (7.6% [95% CI: 7.0-8.2] and 6.4% [95% CI: 5.5–7.3], respectively), living in an urban area (6.6% [95% CI: 6.1–7.0]), having a mother who was young at her daughter's birth (aged 20–24 years, 6.7% [95% CI: 6.3–7.0]) or having Moroccan ethnicity (6.6% [95% CI: 6.1–7.0]). Compared to these variables, Christian conservativeness contributed less to nonparticipation in either prevention program (up to 3.1% [95% CI: 2.7–3.5]), because, generally, conservative Christians do not reject screening.

The PAFs of variables that contributed to participation in none or only one prevention program (− −/− + /+ −; Fig. 2*b*) were lower than the PAFs of variables that contributed to nonparticipation in both programs (− −; Fig. 2*a*). This probably results from the smaller difference between the reference group and the risk groups. Moreover, the probability of nonparticipation in both programs (13%) is smaller than the probability of participation in none or only one prevention program (47%), allowing for a larger relative change in the probability of nonparticipation. The variables that contributed most to participation in none or only one prevention program were the same as contributed to nonparticipation in both programs, except for living in an urban area (Fig. 2*b*).

PAF estimates that were determined using *initiation* of vaccination, not completion of the regimen, showed a very similar pattern (data not shown).

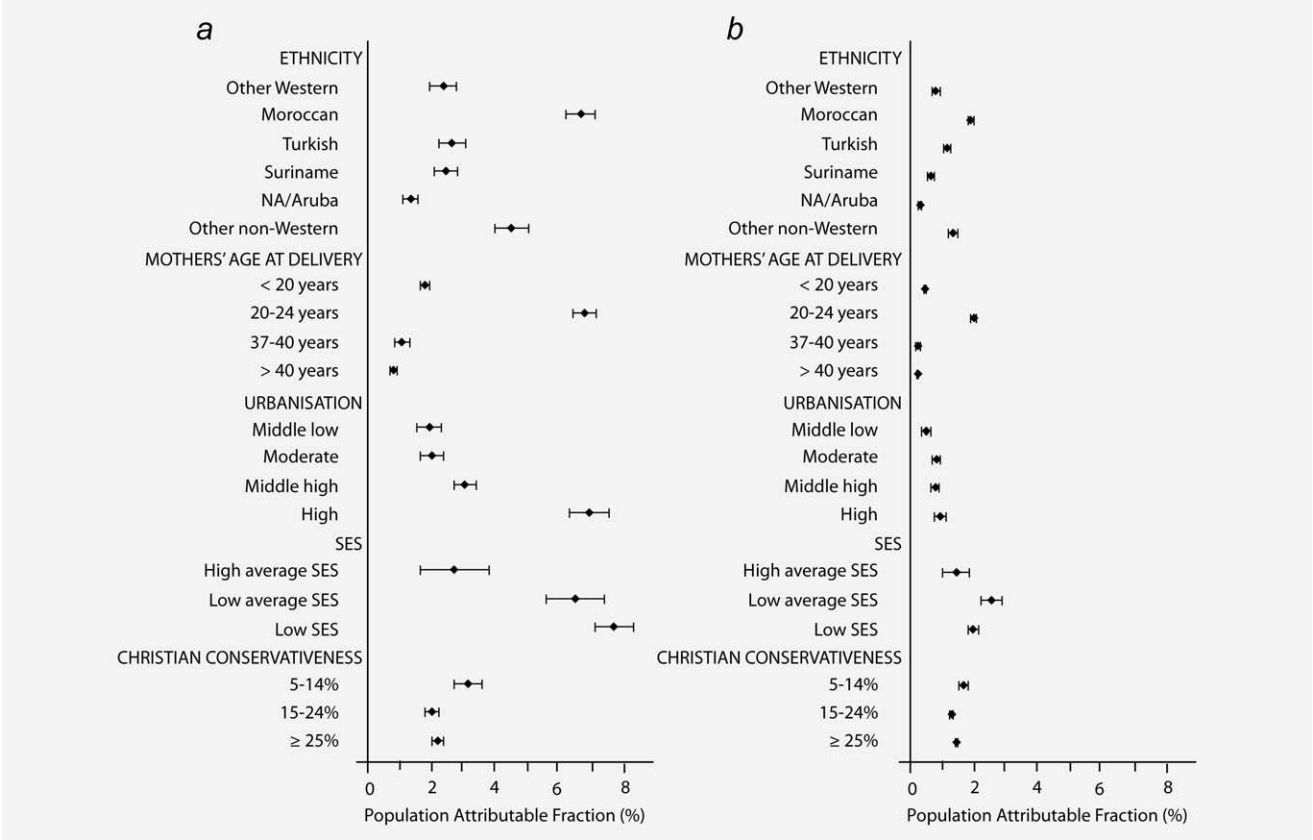

Figure 2. PAF on nonparticipation. The adjusted PAFs and the 95% CI are presented for the different categories of ethnicity, mother's age at delivery, degree of urbanization, SES and Christian conservativeness. Reference categories are not presented, as these are by definition zero. (*a*) PAF on nonparticipation in both prevention programs (− −) compared to participation in any program (− +/+ −/+ +); (*b*) PAF on participation in none or only one prevention program (− −/− + /+ −) compared to participation in both programs (+ +). NA = Netherlands Antilles.

Discussion

To our knowledge, this is the first study to use nationwide data to estimate the association between girls' HPV vaccination status and their mother's screening participation. We quantified the effect of the positive association between girls' vaccination and their own future screening on the impact of cervical cancer prevention by means of a simulation model. Furthermore, we identified risk groups on which interventions should be focused to increase the impact of cervical cancer prevention programs.

We observed a significant positive association between participation in HPV vaccination and cervical screening, indicating selective uptake of the programs. Still, results indicated that the vaccination program will reach a considerable percentage of girls who, based on their mother's behavior, are at risk of nonparticipation in screening. With combined vaccination and screening, 13% are expected not to participate in any prevention program, compared to 23% nonparticipation if screening alone was available. The positive association we observed between completion of HPV vaccination and participation in screening was similar to the findings in the United States (OR: 1.42 [95% CI: 1.31–1.54])[11] despite the differences in health-care systems. In Flanders, Belgium, an even stronger positive association was observed between *initiation* of vaccination and screening participation (OR: 4.5 [95% CI: 3.5–5.9]). However, HPV vaccination was self-initiated, as no centralized vaccination policy was in yet place, and data were obtained from a large Christian health insurance fund,[12] not from a government database.

Ignoring the association between participation in the vaccination and screening programs led to a slight overestimation of the population-level effectiveness of cervical cancer prevention, but the impact was negligible. The overestimation of the absolute number of prevented cases was small for the Netherlands, where a high screening coverage was established. In countries with a lower screening coverage, ignoring the association would lead to a larger overestimation of the *absolute number* of prevented cases. The corresponding cost-effectiveness estimates for the introduction of HPV vaccination could therefore be too optimistic in models that assume random participation.

Screening history of the mothers was known only for 2005–2010, and we therefore had to make assumptions on the life-time and per-screening-round probabilities. Besides, we were not able to distinguish whether the OR accounted for an association between completion of vaccination and participation in screening at least once in a life-time or participation at each screening-round. These uncertainties probably had little

effect on the results. However, as HPV vaccination was implemented only recently, and we had to base the future screening of girls on a 5-year screening history of their mothers, our findings should be considered tentative.

Our study assumes that the mother's screening behavior is predictive for a girl's participation in screening in the future. Although sociological literature indicates that mother's attitude is predictive for her daughter's attitude in adulthood,[9,10] we cannot be sure whether our results resemble the true participation of the girls in the future, as several other factors affect HPV vaccine uptake, such as awareness of HPV.[34] As no better proxy is currently available, we think that the mother's screening behavior can provide valuable insights.

Various factors can affect the future participation in both vaccination and screening programs, changing their preventive impact. At present, Dutch coverage by HPV vaccination is low compared to childhood vaccination and, in 2011, uptake remained lower than anticipated (girls aged 1997: 52.5%),[35] but participation might increase over the years. It is unknown whether vaccination uptake by girls will negatively affect their future screening, for example by giving them a false sense of security.[34,36,37] If vaccinated women were to decrease their screening participation, there might be a higher incidence rate of high-risk cervical neoplasia, which can progress into invasive cervical cancer,[37,38] making the overall effect of prevention HPV vaccination less cost-effectiveness.[16] In May 2011, the Health Council of the Netherlands recommended changing the tests for cervical cancer screening from Pap smears to hrHPV tests, which detect the presence of high-risk HPV.[39] Although screening participation has been constant over time in the Netherlands,[2] this adaptation may affect behavior, as it emphasizes the infectious nature of the causal agent of cervical cancer. On the other hand, such a decrease in screening might be countered by an increase if, as now discussed, a self-sampling procedure is provided to women who avoid screening in a doctor's office.[39] Clearly, it is necessary to monitor long-term participation in both prevention programs.

The effectiveness of the programs can be further increased by focusing interventions on risk groups for nonparticipation. The main risk groups recognized by our study were girls with non-Dutch backgrounds, who live in urban neighborhoods with low SES, who live in a Christian conservative municipality or girls whose mothers were young at delivery. Note that ethnicity data were missing for 71% of our subjects. Its lack was not related to vaccine coverage, screening participation or the percentage of different ethnic groups in the neighborhoods and the distribution of combined participation of the large group with unknown ethnicity was similar to the distribution among Dutch girls. Though, non-Dutch girls were slightly overrepresented in our study (29%) compared to the Dutch population (22%).[22] Therefore, no strong conclusions can be drawn from that result. Nevertheless, ethnic background, Christian conservativeness and SES are important determinants of full vaccine uptake among children in the Netherlands.[24,40] Furthermore, living in an urban area or an area with a moderate–low income is a risk factor for nonparticipation in cervical cancer prevention.[12,19] As lower socioeconomic groups and non-Dutch women are at higher risk of developing cervical cancer,[20,41,42] it is important to encourage their participation.

Although in-depth research is needed to elucidate the reasons for their nonparticipation, it likely results from lack of knowledge about HPV[43] or fear that HPV vaccination will promote promiscuity, early sexual activity or risky sexual behavior.[44,45] Participation increases with education on the need for cervical screening as well as HPV vaccination, with greatest gain among communities at high risk for nonparticipation when local providers are active in the campaign.[46,47] The PAFs determined in our study suggest that participation in prevention programs will increase the most if (effective) interventions target low social economic groups living in urban areas, on Moroccan girls, and on girls whose mothers were young at delivery. However, given the rather low PAFs, qualitative studies on determinants of nonparticipation should be conducted.

We showed that it is feasible to match data on vaccination status and screening participation for approximately the entire target group in the Netherlands. As most children in that country live with both parents (80% in 2010)[48] or with their mother (83% after divorce of the parents),[49] we were able to use the girl's address as matching factor. Nevertheless, matching was unsuccessful for 11%, possibly owing to recent relocation or because the girl did not live on the same address as her mother. As the vaccination coverage among excluded girls was lower compared to included girls, the study may have excluded the population most prone to nonparticipation in both vaccination and screening. This may have led to underestimation of the association between vaccination and screening participation, resulting in underestimation of the effect of the association on modeled estimates and to underestimation of the PAFs.

Conclusions

Using nation-wide registries, we demonstrated that a significant part of potential nonscreeners can be reached through vaccination, if girls' participation is equal as their mothers'. Including this positive association in our simulation model led to a slightly lower estimated impact of the two prevention programs combined, compared to a model that assumed no association. These findings can elucidate the ongoing discussion on the possibly selective uptake of HPV vaccination and cervical screening.

The effectiveness of both programs can be increased further by tailoring interventions to groups at risk for nonparticipation: girls with non-Dutch backgrounds who live in urban areas with low SES or whose mothers were young at delivery. As vaccination and screening participation may change in the future, long-term participation in both programs should be monitored, and our study should be repeated at a later stage.

Overall, the two cervical cancer prevention programs are likely to complement each other, ensuring the cost-effectiveness of HPV vaccination.

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