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Like mother, like daughter? Mother's history of cervical cancer screening and daughter's Human Papillomavirus vaccine uptake in Flanders (Belgium)

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ABSTRACT

Objective: We investigated whether and to what extent the uptake of the Human Papillomavirus (HPV) vaccine by girls aged 12–18 was related to the cervical cancer screening history of age-appropriate older female household members (assumed to be their mothers) in Flanders (Belgium).
Methods: We studied administrative records on 127,854 female members of the National Alliance of Christian Mutualities, which is the largest health insurance fund in Flanders. Reimbursement data for HPV vaccination of girls for the period 2007–2009 were linked with reimbursement data for cervical cancer screening of their mothers in the three preceding years. A multilevel logit model was used to study associations between both preventive behaviors. In the model we controlled for both the girl's and the mother's age, the province of residence and the socio-economic background of the family.
Results: A clear association between a mother's history of participation in cervical cancer screening and her daughter's HPV vaccination initiation was found. The conditional odds of HPV vaccination initiation were more than 4 times higher for girls whose mother had one Pap test than for girls whose mother had none (odds ratio [OR] = 4.5; 95% confidence interval [CI] = 3.5–5.9). For girls whose mother had three or more Pap tests, the conditional odds were 16 times higher than for girls whose mother did not have any pap tests ([OR] = 16.0; 95% [CI] = 12.1–21.2). The effect of screening (having received 1 pap smear as compared to none) was larger for girls living in neighborhoods with the lowest median income ([OR] = 6.0, 95% [CI] = 3.6–10.1).
Conclusion: In a situation where both cervical cancer screening and HPV vaccination are opportunistic, we found evidence that these preventive behaviors cluster within families.

1. Introduction

At present two preventive strategies exist in Flanders (the northern part of Belgium) for the prevention of cervical cancer: cytological screening (Papanicolaou (Pap) smear tests) on the one hand, and vaccination against Human Papillomavirus (henceforth: HPV vaccination) on the other. A relationship between a mother's cervical cancer screening and her daughter's HPV vaccination was described in the US, where the mother's testing history was associated with the daughter's likelihood for vaccination across ethnic and neighborhood socioeconomic strata (overall odds ratio = 1.42) [1].

The quadrivalent and the bivalent HPV vaccines (Gardasil® en Cervarix®) were licensed in Belgium in September 2006, and

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September 2007, respectively. During the first 2.5 years after their introduction on the Belgian market (from January 2007 to June 2009), no centralized vaccination policy was in place (only in September 2010 school-based vaccination was introduced for 11–12 year old girls in Flanders): HPV vaccination had to be initiated by the girl/woman, her general practitioner, pediatrician or her gynecologist. In the latter three cases, it could be initiated during a consultation for unrelated medical reasons. The vaccines were partly reimbursed by the national health insurance and by the sickness funds. The cost per dose for the vaccines was 124.16 euro. For certain age groups the national health insurance reimbursed 113.36 euro per dose, for other groups sickness funds reimbursed 50 euro per dose. Reimbursement rules varied over the period of analysis and were determined purely by the age of the girl [2].

The Flemish program for cervical cancer screening is based on the European guidelines. Hence, one Pap smear or liquid-based cytology sample every 3 years is recommended for women of 25–64 years of age. The implementation of the program is entrusted to the provinces that are instructed to make women and physicians aware of the screening policy. From 2004 to 2006, 4 out of 5 provinces undertook some form of activity with regard to cervical cancer screening, but to a large extent the screening was performed at the initiative of women or general practitioners / gynecologists [3–5]. The most recent available data on cervical cancer screening date from the year 2000, when in Flanders the screening coverage for women aged 25–64 was 57%. At the same time, substantial overuse of Pap smears was reported, the modal screening interval being 1 year [5].

In this article we investigate whether in Flanders an association exists between the uptake of the first dose of a HPV vaccine (HPV vaccination initiation) by girls aged 11–18 and the cervical screening behavior of age-appropriate older female household members (assumed to be their mothers). We also look whether HPV vaccination completion (having received a complete regimen of 3 doses) is related to the mother's screening behavior. By using multilevel analysis we explicitly model the clustering of vaccination behavior within families.

2. Materials and methods

2.1. Sample

We analyse data from the National Alliance of Christian Mutualities (henceforth: NACM), the largest sickness fund in Flanders covering 53% of the Flemish population. All analyses were carried out at the NACM under supervision of a medical advisor.

We selected female members of the NACM aged 11–18 (years of birth 1989–1996) who were member of the NACM on December 31st 2006 and who were living in Flanders. Out of these girls, we selected those who continued membership of the NACM during the whole period of analysis, i.e. until June 30th 2009. We identified each girl's likely mother using the unique household number that is assigned annually to each member of a Belgian sickness fund ([6], as at January 2007. To identify potential mothers with a full screening history, we selected all female members with the same unique household number, who were at least 16 years older, but less than 45 years older than the girl (as per Chao et al. [1]), and who were members of NACM continuously for three years prior to 2007. Finally, we excluded girls for whom one of the predictor variables (see further for a description) was missing. For most of these girls, the missing variable was the median income of the neighborhood. Fig. 1 documents the selection process.

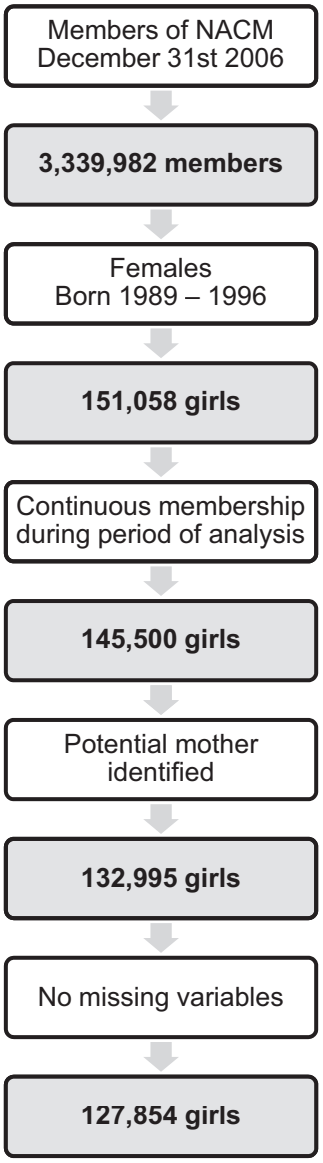

Fig. 1. Overview of the selection process.

2.2. Variables

Our main outcome variable was HPV vaccination initiation between January 1st 2007 and June 30th 2009. We also considered HPV vaccination completion (having received a complete regimen of 3 doses of the vaccine between January 1st 2007 and June 30th 2009) for girls who received their first dose before November 2008 (leaving them at least 9 months to complete the vaccine regimen within our period of analysis, the recommended interval between the first and the last dose being 6 months).

Data on mothers' cervical screening behavior were extracted from the reimbursement claims as the number of Pap smears collected from 2004 to 2006. The reimbursement claims contain information on all medical acts related to screening but not on cytological results. Because results were not available to us, we could not infer whether a screening frequency of more than 1 per 3 years was due to (unnecessary) over-screening, a follow up of cytological abnormalities, treatment of cervical lesions or unsatisfactory specimen. If there was more than one potential mother in the household (544 cases), the mean number of Pap smears was used for the

Table 1
Comparison of characteristics of the girls affiliated to the NACM who were included and excluded.

		Included (N = 127,854)	Excluded (N = 23,204)
		N (%)	N (%)
Year of birth (Age in 2007)			
	1989 (18)	16,028 (12.54)	3,056 (13.17)
	1990 (17)	16,672 (13.04)	2963 (12.77)
	1991 (16)	16,989 (13.29)	2863 (12.34)
	1992 (15)	16,871 (13,20)	2871 (12.37)
	1993 (14)	16,259 (12.72)	2819 (12.15)
	1994 (13)	15,217 (11.90)	2773 (11.95)
	1995 (12)	15,044 (11.77)	2869 (12.36)
	1996 (11)	14,774 (11.56)	2990 (12.89)
Preferential treatment			
	Yes	5,718 (4.47)	1955 (8.51)
	No	122,136 (95.53)	21,009 (91.49)
Province			
	Antwerp	34,158 (26.72)	5831 (25.16)
	Limburg	16.563 (12.95)	3266 (14.09)
	East-Flanders	28,394 (22.21)	5800 (25.02)
	West-Flanders	29,044 (22.72)	5001 (21.58)
	Flemish Brabant	19,695 (15.40)	3279 (14.15)
Median income neighborhood			
	Quintile 1 (lowest)	17,581 (13.75)	2852 (18.29)
	Quintile 2	24,190 (18.92)	3063 (19.64)
	Quintile 3	25,358 (19.83)	3022 (19.38)
	Quintile 4	28,344 (22.17)	3215 (20.61)
	Quintile 5 (highest)	32,381 (25.33)	3445 (25.33)

Note: All associations were found significant ($p < 0.0001$).
[a] The following girls were included in the study: girls that continued membership of the NACM during the whole period of analysis, for whom an age-appropriate female household member could be identified with a full screening history, and for whom values of all predictor variables could be collected.
[b] The quintiles are calculated for the whole of Flanders: each quintile encompasses 20% of all tax declarations in Flanders.

analysis. Interaction effects of screening behavior with other predictors were assessed.

Key variables for analysis included year of birth of the daughter, age of the mother and province of residence.

Two predictors reflecting the socio-economic status of the family were also added to the model: the median income of the neighborhood in which they were living (in quintiles) [7], and a variable indicating whether at least one person in the family was entitled to preferential treatment or not. These two variables were correlated (Pearson correlation coefficient = −0.12 ($p < 0.001$)), but since the correlation was modest, both were included. "Preferential treatment" is a right that certain categories of people enjoy within the Belgian health insurance. It implies they pay lower co-payments for health care. Two basic grounds for preferential treatment eligibility existed at the time of the analysis. First, people receiving certain social benefits (social assistance, guaranteed income for elderly, guaranteed income for disabled), as well as their partners and descendants, were automatically entitled to preferential treatment. Second, certain categories of people (most importantly: orphans, widows, widowers, disabled, elderly, long term unemployed, children with severe mental or physical illnesses) as well as their partners and descendants were eligible after an income test had shown that their household income was below a certain threshold. Because in both cases a low household income is a direct or indirect condition for preferential treatment, we can use it as an indicator for the socio-economic status of the family. We categorized a girl as being eligible for preferential treatment if at least one person in the household was eligible (indicating a low household income) on December 31st 2006.

2.3. Statistical analyses

We first looked at the bivariate associations between HPV vaccination initiation/completion and some characteristics of interest. The significance of these associations was assessed by means of the (two-sided) chi-square test.

Then, the data for HPV vaccination initiation were analysed using a multilevel logistic regression model [8], which is able to account for clustering, since the girls whose behavior we were analyzing were clustered within households, and a substantial part of them were sisters 'sharing' the same mother. The explanatory variable at the level of the girl was her year of birth. At the level of the household, we included age of the mother, screening behavior of the mother, province of residence, preferential treatment and income quintile of the neighborhood of residence. Interaction effects between a girl's year of birth and the screening status of her mother and between the income quintile of the neighborhood and the screening status of the mother were also assessed.

The estimated odds ratios from this random effects model are conditional odds ratios, i.e. they control for the between household heterogeneity. These conditional odds are larger than the odds ratios calculated from the marginal model (without random intercept), because in the marginal model the effect of the predictor variables is masked by the heterogeneity between families. However the odds ratios in the marginal model can be approximated using a standard method [9] in order to facilitate comparisons with other studies in which no multilevel design was used.

All analyses were performed using SAS®, version 9.1.

3. Results

3.1. Characteristics of the study population

In Table 1 we give an overview of the demographic characteristics of the girls included in and excluded from the study. Girls included in the study on average lived in neighborhoods with higher median income, and were less often eligible for preferential treatment compared to the girls that did not meet our inclusion criteria.

For the 127,854 girls used in the analysis 105,541 potential mothers were identified. Of these mothers, 33.06% (N = 34,888) had not received any Pap smears during 2004–2006, 28.79% (N = 30,383)

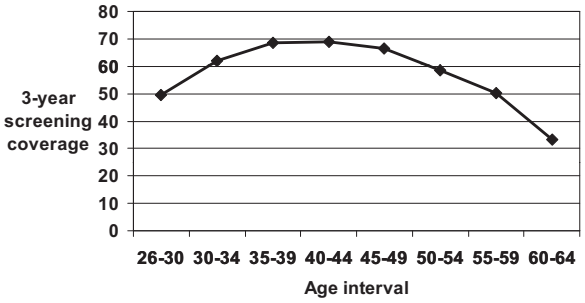

Fig. 2. 3-year screening coverage of mothers according to age interval.

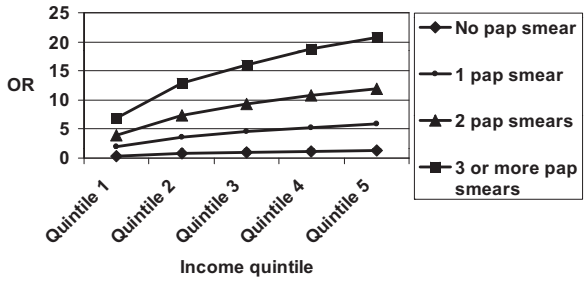

Fig. 3. Estimated conditional odds ratios for HPV vaccination initiation according to screening status of the mother and income quintile of the neighborhood.

had received one, 22.11% (N = 23,338) had received two, and 16.04% (N = 16,932) had received three or more. The 3-year screening coverage (defined as the proportion with at least one Pap smear over the three years of analysis) was 67%, which is 10 percentage points higher than the 3-year screening coverage for the total Flemish female population aged 25–64 between 1996 and 2000 [5]. Furthermore, as can be seen from Fig. 2, the screening behavior of the mothers was strongly dependent on their age. Finally, the screening behavior also differed according to median income of the neighborhood: in neighborhoods with the lowest median income the 3-year screening coverage of the mothers was 62%, whereas in neighborhoods with the highest median income it was 71%. The 3-year screening coverage of the mothers according to province of residence varied between 65 and 69%.

Table 2
HPV vaccination initiation according to characteristics of interest and results of the random intercept logistic regression model for HPV vaccination initiation between January 2007 and June 2009.

			Bivariate analyses		Random intercept logistic regression	
			Vaccination initiation N (%)	P (chi-square)	OR	P
Constant					27.36	<0.0001
Daughters						
	Year of birth (Age in 2007)	1989 (18)	3557 (22.19)	<0.0001	0.00	<0.0001
		1990 (17)	9275 (55.63)		0.04	<0.0001
		1991 (16)	9470 (55.74)		0.04	<0.0001
		1992 (15)	13,968 (82.79)		(Base)	(Base)
		1993 (14)	12,312 (75.72)		0.29	<0.0001
		1994 (13)	10,109 (66.43)		0.10	<0.0001
		1995 (12)	7393 (49.14)		0.02	<0.0001
		1996 (11)	3542 (23.97)		0.00	<0.0001
Household						
	Age mother (centered)[a]				1.01	0.2423
	Age mother squared (centered)[a]				0.99	<0.0001
	Number of pap smears mother	0	19,038 (45.24)	<0.0001	(Base)	(Base)
		1	20,421 (55.05)		4.52	< 0.0001
		2	17,045 (60.21)		9.24	< 0.0001
		≥3	13,122 (64.43)		16.03	< 0.0001
	Preferential treatment		1992 (34.84)	<0.0001	0.13	< 0.0001
	Median income neighborhood	Quintile 1 (lowest)	7832 (44.56)	<0.0001	0.33	< 0.0001
		Quintile 2	12,696 (52.48)		0.76	0.0050
		Quintile 3	14.015 (55.27)		(Base)	(Base)
		Quintile 4	16,184 (57.07)		1.14	0.1639
		Quintile 5 (highest)	18,899 (58.38)		1.29	0.0070
	Province					
		Antwerp	18,772 (54.96)	<0.0001	(Base)	(Base)
		Limburg	9735 (58.78)		1.74	<0.0001
		East-Flanders	14,932 (52.59)		0.68	<0.0001
		West-Flanders	14,791 (50.92)		0.61	< 0.0001
		Flemish Brabant	11,396 (57.86)		1.16	0.0123
Interaction effects						
	Quintile 1 * screened				1.29	0.0352
	Quintile 2 * screened				1.06	0.6572
	Quintile 4 * screened				1.03	0.8314
	Quintile 5 * screened				1.00	0.9805
	1989 * screened				0.56	0.0001
	1990 * screened				0.70	0.0063
	1991 * screened				0.70	0.0082
	1993 * screened				1.01	0.9341
	1994 * screened				0.76	0.0474
	1995 * screened				0.50	<0.0001
	1996 * screened				0.29	<0.0001
Household level variance					16.95	<0.0001

[a] As is common in multilevel analysis, the age of the mother and the age of the mother squared were centered around the mean, meaning for every observation the (squared) mean age of all mothers was subtracted from the observation's (squared) age.

3.2. HPV vaccination initiation

In Table 2 we present the percentage of girls who initiated HPV vaccination between January 2007 and June 2009 according to some characteristics of interest. Vaccination behavior of girls was strongly associated with their mother's screening behavior. Only 45% of the girls whose mother had not received any Pap smears in the period 2004–2006 had initiated HPV vaccination by June 2009, whereas in the group of girls whose mother had received 1 Pap smear, this was 55%. Girls whose mother had more than the recommended number of Pap smears were even more likely to have initiated HPV vaccination (with 60 and 64% of the girls having initiated vaccination when their mothers had received 2 or "3 or more" Pap smears, respectively). Both girls from neighborhoods with lower median incomes and girls eligible for preferential treatment had a lower chance of having initiated HPV vaccination. Finally, we found large differences in the percentage of girls who had initiated vaccination according to their year of birth, with girls born in 1992 having the highest vaccination uptake.

The results of the multilevel logistic regression are shown in Table 2. The "reference girl" in our analysis was born in 1992 (median birth year), was not eligible for preferential treatment (majority), lived in the province of Antwerp (majority), in a neighborhood within the third quintile of median incomes in Flanders (median) and had a mother of 43 years old (mean age of mothers).

We found that the screening behavior of the mother was strongly associated with the vaccination behavior of the daughter. The conditional odds of HPV initiation of girls whose mother had received 1 Pap smear in the three years before the HPV vaccine became reimbursed were higher than the conditional odds of girls whose mother was not screened (odds ratio [OR] = 4.5, 95% confidence interval [CI] = 3.5, 5.9). When the mother had received 3 or more Pap smears, the conditional odds for vaccination initiation of her daughter were even 16 times higher than in the case she was not screened ([OR] = 16.0, 95% [CI] = 12.1, 21.2). The significant cross level interactions between year of birth of the girl and positive screening status of the mother (having had at least 1 Pap smear) indicated that for girls not born in 1992, the effect of the mother's screening on the daughter's vaccination initiation was somewhat smaller. However, the parameter estimates of these interactions were substantially smaller than the direct effects of screening, so the overall effect of screening on vaccination initiation remained large and significant for all birth years. With regard to the interaction effect between income quintile of the neighborhood and screening status of the mother, only the interaction between the lowest income quintile and screening status was significant. This indicated that the effect of screening (having received 1 pap smear instead of none) was larger in the lowest income neighborhoods ([OR] = 6.0, 95% [CI] = 3.6–10.1) (Fig. 3).

The conditional odds of vaccination initiation further differed according to year of birth of the girl, with the highest conditional odds for girls born in 1992. Also, the highest conditional odds were found in the provinces of Antwerp, Limburg and Flemish Brabant. Furthermore, girls coming from neighborhoods with lower median income, and girls with preferential treatment, had lower conditional odds of vaccination initiation.

Calculating the parameter estimates in the marginal model (without random effects) we found that these parameter estimates were 2.49 times smaller than in the random effects model. According to the marginal model, then, the odds of HPV vaccination initiation of girls whose mother had received 1 Pap smear in the three years before the HPV vaccine became available were 1.8 times higher than the odds of girls whose mother had not received any Pap smears. The odds of HPV vaccination initiation of girls whose mother had received 3 or more smears were 6.4 times higher than the odds of girls whose mother was not screened.

3.3. HPV vaccination completion

HPV vaccination completion (given a girl had initiated vaccination) was high: 90% of the 50,409 girls that started with HPV vaccination before November 2008 completed the regimen by June 2009. The percentage varied from 89% for girls whose mother had not received any pap smears in 2004–2006 to 92% for girls whose mother had received three or more pap smears. Because of this weak association with the screening status of the mother, we did not perform further (multilevel) analyses for vaccination completion.

4. Discussion

We found that HPV vaccination initiation by daughters was associated with cervical screening behavior of their mothers, which is in line with findings from the United States [1]. Moreover, the more frequently a mother received a Pap smear, the more likely her daughter was to initiate HPV vaccination. The association was stronger for girls living in neighborhoods with the lowest median incomes. A clear social gradient was found. The highest odds of vaccination initiation were seen in the provinces of Antwerp, Limburg and Flemish Brabant, a result that corresponds to results from other studies [10]. The large differences in vaccination uptake according to the girls' year of birth are explained in more detail elsewhere [2]. However, they are mainly the result of differences in reimbursement regime over time and an age effect, whereby older girls tend to get vaccinated more (possibly because as they approach the age limit of reimbursement eligibility (and proven efficacy of the vaccine) they tend to procrastinate less), and an information campaign by the NACM. The large household variance (16.95) indicates that substantial heterogeneity in vaccination initiation between households remained unexplained after taking into account our predictor variables.

There may be several reasons why screening and vaccination behavior cluster within families. One can think of between-family differences in the underlying attitudes, beliefs or values towards preventive health care or in the fear for cervical cancer [11,12]. The behaviors might also cluster because they both take place in the same social, economic and physical environment that can be either stimulating or restraining for preventive health behaviors [13,14] Further, it is possible that through contacts with the gynecologist or general practitioner within the framework of cervical cancer screening mothers are encouraged to get their daughter vaccinated [11,15]. Additionally, families from higher social classes may be more receptive to information or media campaigns on screening and vaccination [16].

4.1. Our study is subject to several limitations

First, our sample is not entirely representative of the total Flemish population: although the age and sex profile of NACM members reflect the profile in the general population quite well, members of the NACM on average come from somewhat richer neighborhoods [17]. Religious background nowadays is not a strong predictor of membership of a specific sickness fund, and even if it was, the number of members for whom their religion would impact on HPV vaccination uptake is extremely low. However we cannot entirely preclude that NACM members, due to other unobserved characteristics, have a different likelihood of being vaccinated than members of other sickness funds. This study therefore should be seen as a (large-scale) case-study of a large part of the Flemish population.

Second, a disadvantage of working with the reimbursement data is that only reimbursed doses of the HPV vaccine are recorded. This could be problematic for the period before HPV vaccines were reimbursed, the two month period between November 1st 2006 (introduction of the first HPV vaccine on the market) and December 31st 2006. However, we do not believe that this poses a major problem because the number of HPV vaccine doses sold during the two first months after market introduction in Belgium was very small [18].

A third limitation is that we did not have access to direct measures of individual (or family-level) socio-economic status (SES). This decreases the ability of our study to measure its impact. However, by using two different indicators that reflect different aspects of the social background, we believe that we do capture a reasonable part of the differences in socio-economic status that exist between individuals and families in our sample.

4.2. Despite of these limitations, the analysis also has important strengths

First, working with administrative data helps to avoid problems common in surveys, such as a potential recall bias and difficulties to gather complete and reliable information. Indeed, the cervical screening coverage computed from administrative health insurance data for Flanders was substantially lower than the estimates derived from national health interview surveys [5]. Also, in adolescent vaccination surveys necessary documents are often missing and respondents have problems recalling the necessary information, although this problem has diminished over the past few years [10].

Second, the unique household number allowed us to link information on mothers' screening status to daughters' vaccination status.

Third, multilevel analysis allowed us to control for clustering of the behavior of sisters within families. As we have shown, the conditional odds ratios calculated from the random effects model were considerably larger than the odds ratios in a model in which random effects are not taken into account.

Finally, because of administrative procedures, representative administrative data for Belgium or Flanders only become available with a substantial time lag. Working with the data of the NACM allowed us to analyse data on HPV vaccination shortly after the introduction of the vaccine for a substantial part of the Flemish population. In a period in which governments of many European countries are deciding whether and how to organize HPV vaccination [19], important lessons can be drawn from countries where HPV vaccination was already implemented.

Further research uncovering the causes of the observed patterns is important because, as indicated above, clustering of cervical screening and HPV vaccination within families might have important consequences for the effectiveness and cost-effectiveness of screening and vaccination programs. Since family members have a large influence on children's and adolescent's health attitudes and behavior [12,14,20,21], and since health behaviors are carried over from adolescence into adulthood to a substantial extent [22,23], it is plausible that daughters of non-screening mothers will not participate in screening once they become adults, either. Moreover, as we have shown, they have a higher chance of remaining unvaccinated, too. When a subgroup of the population is not vaccinated during adolescence nor screened during adulthood, the effectiveness, equity and cost-effectiveness of combined HPV screening and vaccination programs could decrease substantially [24–26]. This is especially so if this subgroup acquires HPV infection earlier in life (and hence develops cervical cancer earlier) than average, as would be the case for people with lower socio-economic status, who are sexually active earlier in life [27,28]. Centralized funding and organization of vaccination and screening might help to minimize the risks of widening inequities and suboptimal cost-effectiveness. In the absence of such centralized policies or when budgets are limited, the observed predictors of HPV vaccination initiation might be used for tailor-made vaccination campaigns: HPV information messages could for example focus on lower SES families with mothers having incomplete screening histories.

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