Preventive Medicine 120 (2019) 26–33

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Mode of HPV vaccination delivery and equity in vaccine uptake: A nationwide cohort study

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ARTICLE INFO

Keywords:
HPV vaccine
Uptake
Vaccination delivery
Socioeconomic status
Migration
Disparity

ABSTRACT

Ten years after its introduction, equity in human papillomavirus (HPV) vaccine uptake remains unattained, not least for the groups at highest risk of cervical cancer. In Sweden, three different delivery modes of the vaccine have been in effect since May 2007. We used this as a natural experiment to investigate girls' HPV vaccine uptake in relation to parental country of birth and socioeconomic characteristics, by mode of delivery. Our nationwide study cohort comprised 689,676 girls born between 1990 and 2003. Data on HPV vaccination of the girls and parental birth/socioeconomic characteristics were retrieved from national registers. We examined the association between girls' vaccine uptake and parental characteristics, stratified by mode of delivery. The cumulative uptake of at least one dose of HPV vaccine was 37%, 48% and 79% for subsidised opportunistic, free-of-charge catch-up outside-school and free-of-charge school-based vaccination, respectively. In the subsidised vaccination, having parents born outside of Sweden, with low education and low family income was strongly associated with lower uptake [HR (95% confidence interval (CI)) = 0.49 (0.48–0.50), 0.32 (0.31–0.33), 0.53 (0.52–0.54), respectively]. The associations were partially reduced in catch-up outside-school, and strongly reduced in school-based vaccination delivery [HR (95% CI) =0.82 (0.81–0.83), 0.92 (0.91–0.94), 0.87 (0.85–0.88), respectively]. Free-of-charge school-based HPV vaccination achieved the highest uptake and displayed the least disparity in country of birth and socioeconomic background of the parents. This appears to be the most effective and equitable delivery mode for reaching high population vaccination coverage, including high-risk groups for cervical cancer.

1. Introduction

Human papillomavirus (HPV) vaccine has gradually been approved in numerous countries worldwide during the latest decade. Yet coverage varies substantially and systematic disparities in uptake (Polonijo and Carpiano, 2013; Roberts et al., 2011; Rondy et al., 2010; Slåttelid Schreiber et al., 2015) may consequently aggravate inequality of HPV-related disease prevention. A migration background (Azerkan et al., 2008) and low socioeconomic status are established risk factors for cervical cancer (Clegg et al., 2009; Devesa and Diamond, 1980; Hakama et al., 1982; Singh and Jemal, 2017), yet of concern these very groups tend to participate less in HPV-vaccination (Polonijo and Carpiano, 2013; Roberts et al., 2011; Rondy et al., 2010; Slåttelid Schreiber et al., 2015). Even though individuals with migration background and low socioeconomic status might be particularly difficult to reach, more equitable vaccination may be achieved through improving the model of delivery. Mode of delivery has been shown to reduce socioeconomic differences in participation for other health services, such as childhood immunisation and screening (Bishai et al., 2002; Lee et al., 2010). A recent review showed that school-based delivery generally achieved higher HPV vaccination coverage, but the comparisons were effectively made mostly between different countries, and the findings could therefore be due to other differences between the compared countries (Paul and Fabio, 2014). Furthermore, few studies have investigated how socioeconomic inequalities may vary by differing mode of delivery of HPV vaccine, and those studies have used single or group-level

Abbreviations: SVEVAC, the Swedish Vaccination Register; COB, country of birth

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https://doi.org/10.1016/j.ypmed.2018.12.014
Received 8 June 2018; Received in revised form 31 October 2018; Accepted 24 December 2018
Available online 27 December 2018

socioeconomic indicators (Lefevere et al., 2015; Musto et al., 2013). More comprehensive evidence is needed as to which mode of delivery could best promote uptake and reduce inequity in HPV vaccination coverage.

Several modes of HPV-vaccine delivery, varying by administrative setting and personnel costs, have been implemented in Sweden since the introduction of the vaccine. Subsidised opportunistic vaccination started in May 2007, targeting girls aged 13–17 years. The cost was subsidised by the government, leaving the individual payment on average up to 50% of the total vaccine cost (Sundström et al., 2010). HPV vaccination for the primary target age group, i.e. girls aged 10–12 years, was introduced into the National Immunisation Programme in 2010. Since January 2012, a free-of-charge school-based delivery was implemented for the primary target age group, together with a free-of-charge catch-up vaccination to girls born in 1993–1998 with continuous implementation for girls up to age 17 years occurring to some extent until 2014. This staggered implementation is similar to a natural experiment, and enables a comprehensive nationwide evaluation of factors associated with improved uptake, and/or reduced disparity in uptake. During the catch-up vaccination, it has been shown that counties using school delivery of HPV vaccination reached higher uptake (Rehn et al., 2016). Using the Swedish individually-linked healthcare and population registers, we will compare girls' overall uptake of HPV vaccine across three modes of delivery, as well as potential associations with parental country of birth and socioeconomic background.

2. Materials and methods

2.1. Data sources

All data in this population-based cohort study were retrieved from Swedish national registers covering the whole population, linked via the Swedish personal identification number. These registers were the Total Population Register (Ludvigsson et al., 2016), the Cause of Death Register ("Dödsorsaksregistret,", n.d.), the Multi-Generation Register (Ekbom, 2011), the Prescribed Drug Register (Wettermark et al., 2007), the Swedish Vaccination Register (SVEVAC) ("Statistik för HPV-vaccinationer — Folkhälsomyndigheten,", n.d.), the National Vaccination Register and the sociodemographic LISA-Database ("Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym),", n.d.), Details of each respective register are given in Appendix 1.

2.2. Study cohort

Our study included girls eligible for at least one HPV vaccination delivery mode (Fig. 1, Appendix 2), i.e. born between 1990 and 2003, and resident in Sweden between May 2007 (the beginning of HPV vaccination programme) and December 2014 (the end of study period). Girls dead or emigrated before being eligible for the vaccination delivery, or immigrated after becoming eligible for the delivery, or vaccinated before being eligible, were excluded. For the period 2012–2014, a technical issue with anonymous vaccinations was present in SVEVAC, among girls eligible for the catch-up and school-based vaccination. This disables the linkage to their parents. We therefore further excluded girls resident in the five counties out of 21 that had more than 30% anonymous vaccinations during this period (Appendix 3) (Fig. 2).

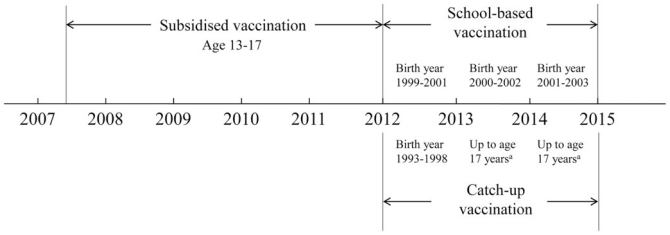

Fig. 1. Time-line of vaccination deliveries, with corresponding ages and birth-cohorts
a. Birth year up to 1998. According to typical implementation of the original recommendation for catch-up vaccination of girls born 1993–1998.

2.3. Exposures and outcomes

Our primary exposure was mode of delivery of HPV vaccination, categorised as subsidised opportunistic, catch-up or school-based vaccination. The subsidised opportunistic vaccination required individual co-payment and was administrated in primary healthcare centres or vaccination clinics; the school-based vaccination was completely free of charge for individuals, and administrated in schools; the catch-up vaccination was also free of charge, but in terms of setting of vaccination it was administrated differently across counties. To clearly distinguish the three delivery modes in terms of individual co-payment/cost and vaccination administration setting, we assessed girls in the counties that offered the catch-up vaccination in and outside of schools (4 and 9 out of 21 counties, respectively) separately. However, two (Jönköping and Värmland) of the four counties administrating in schools had more than 30% anonymous vaccination during 2012–2014 and were thus not eligible for our main analysis. The remaining two counties (Jämtland and Västernorrland) were of medium to smaller size and co-located, which meant data on vaccination was considered too limited to form an independent category fully comparable to other mode of delivery groups. We therefore present our main results without data from the free-of-charge, catch-up vaccination delivered in-school mode, but for completeness we report the latter in the supplementary results (S-Figure-2 in Supplementary Material).

Delivery mode of HPV vaccination was treated as a time-varying exposure, meaning that, if applicable, one girl could contribute to the follow-up time of each (multiple) delivery mode ($-s$) she had been eligible for. Eligibility criteria for each delivery mode are presented in Appendix 2.

Covariates considered included country of birth (COB), level of education and disposable family income of the mother and father, respectively, of the girls in the cohort. COB was primarily categorised into Sweden and "other countries", which were further categorised into 19 regions according to the geographical classification used by the International Agency for Research on Cancer (Parkin et al., 2005). Level of parental education was classified as a) low if the highest schooling was primary education 9 years and below, b) medium if 2–3 years of secondary schooling (similar to senior high-school), and c) high if post-secondary education and above (equivalent to university studies). We used the highest level of registered parental education by the year before the girl was eligible for each delivery mode. The disposable income of the family was retrieved for both mother and father in the year before the girl was eligible and categorised into tertiles derived from the whole population (Appendix 4).

The outcome HPV vaccination status was ascertained as being vaccinated at the date of the first dose in the register(s). Dose completion was assessed by identifying the valid number of times of receiving the vaccine, as described previously (Herweijer et al., 2014).

2.4. Statistical analyses

We used the Kaplan-Meier survival function to plot cumulative incidence (i.e. cumulative uptake) of receiving the first dose of the vaccine over time since eligibility in months, by delivery mode. We presented overall curves for all included counties, because the coverage of HPV vaccination was similar across counties, according to reports from the Public Health Agency of Sweden ("Statistik för HPV-vaccinationer — Folkhälsomyndigheten,", n.d.). We plotted the cumulative uptake

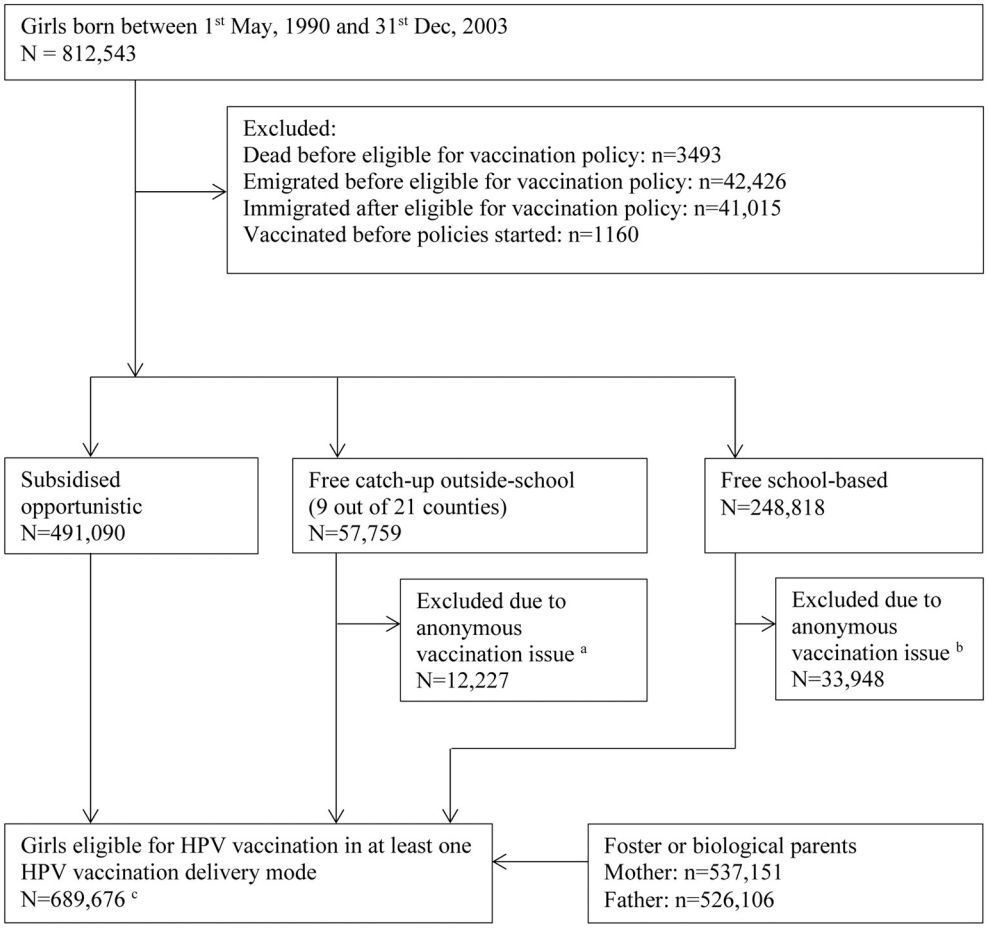

Fig. 2. Study population
a. Girls resident in counties that had more than 30% anonymous vaccination during 2012–2014 (Appendix 3)
b. Girls resident in counties that had more than 30% anonymous vaccination in 2012 (Appendix 3)
c. The number is smaller than the sum of girls in subsidised, catch-up and school-based vaccination, because each girl could be eligible for more than one vaccination delivery mode depending on calendar period, and the categories are thus not entirely mutually exclusive.

among girls eligible for different delivery modes by COB, education and family disposable income of the mother and father (which may differ if parents do not cohabit), respectively. We estimated relative vaccine uptake comparing girls with mothers and fathers born outside Sweden to Swedish-born, medium and low level of education to high level, as well as medium and low level of family disposable income to high level, using Cox proportional hazard models. Crude relative uptake was obtained from univariate Cox models for each vaccination delivery, and the adjusted relative uptake was estimated by multivariate Cox models including all characteristics of the parents as well as county of residence.

Among girls who were vaccinated with the first dose before July 1, 2014, we assessed the proportion of girls completing three doses according to the COB/socioeconomic background of the parents and estimated crude and adjusted odds ratios of dose completion using logistic regression.

To examine potential influence of anonymous vaccination on the association between studied factors and relative uptake, as well as dose completion of the vaccination, we performed sensitivity analyses by restricting the material to counties that had less than 15% anonymous vaccination. To enhance comparability between modes of delivery, we further performed sensitivity analyses for the subsidised and school-based vaccination within the counties that were included in the analysis of the catch-up outside-school vaccination. Finally, we analysed cumulative uptake and dose completion by region of parental country of birth.

3. Results

The study cohort consisted of 689,676 girls, with 537,151 women as foster or biological mothers and 526,106 men as fathers (Fig. 2). Mothers and fathers had a similar distribution in COB and family disposable income, though mothers were of higher education level than fathers (Table 1).

Cumulative uptake of at least one dose of vaccine in the subsidised opportunistic vaccination increased steadily over time and reached

Table 1
Characteristics of the parents of individual girls eligible for HPV vaccination in Sweden during 2007–2014.

	Girls with mother, n[b]	Mother, %	Girls with father, n[b]	Father, %
Country of birth				
Sweden	534,479	77.5	526,509	76.3
Other countries	139,938	20.3	134,516	19.5
Missing	15,259	2.2	28,651	4.2
Education level				
High	255,939	37.1	208,014	30.2
Medium	326,453	47.3	337,006	48.9
Low	80,305	11.6	99,445	14.4
Missing	26,979	3.9	45,211	6.6
Disposable family income level[a]				
High	272,199	39.5	270,174	39.2
Medium	241,962	35.1	231,182	33.5
Low	154,371	22.4	144,264	20.9
Missing	21,144	3.1	44,056	6.4

[a] Definition and cut-off for tertiles is in Appendix 4.
[b] Numbers are presented on the basis of girls.

37% at 58 months after start of eligibility. Cumulative uptake in catch-up vaccination outside of schools reached a slightly higher level (48%), but within a much shorter time period. The school-based vaccination achieved the highest cumulative uptake of 79%, again in a short time period (Table 2, Fig. 3).

Girls with mothers born in Sweden had higher cumulative uptake of HPV vaccine than those with mothers born in other countries. Girls with mothers at high, medium and low level of education and family income had the highest, medium and lowest cumulative uptake, respectively, regardless of delivery mode. The differences in cumulative uptake by COB and socioeconomic characteristics of mothers were greatest in subsidised opportunistic vaccination, followed by catch-up vaccination, and smallest in school-based vaccination (Fig. 4). After adjusting for county of residence and other studied factors, in the subsidised vaccination, having a mother born outside of Sweden, of low education and family income were factors strongly associated with lower cumulative uptake [HR (95% confidence interval (CI)) = 0.49 (0.48–0.50), 0.32 (0.31–0.33), 0.53 (0.52–0.54), respectively]. The associations with maternal characteristics were partially reduced in catch-up outside-school [HR (95% CI) = 0.69 (0.66–0.72), 0.70 (0.66–0.74), 0.78 (0.75–0.81), respectively], and strongly reduced in school-based vaccination [HR (95% CI) = 0.82 (0.81–0.83), 0.92 (0.91–0.94), 0.87 (0.85–0.88), respectively] (Table 3). The association between vaccine uptake and paternal characteristics were similar as those observed for maternal such (S-Figure-1, S-Table-3 in Supplementary Material).

Among girls receiving the first dose, the proportions of completing three doses in the subsidised, catch-up outside-school and school-based vaccination were 89%, 66% and 82%, respectively (Table 2).

Girls with mothers born outside of Sweden, having the lowest level of education and family income exhibited a slightly lower dose completion in three delivery modes, with differences ranging from 1.4%–8.2% (S-Table-2 in Supplementary Material). The lower dose completion associated with foreign-born and low education tended to be more pronounced in catch-up vaccination compared with subsidised and school-based delivery, but the differences between delivery modes were not statistically significant (Table 4). Results for fathers were similar to those for mothers (S-Table-4 in Supplementary Material).

In sensitivity analyses limited to counties with less than 15% anonymous vaccinations, results were not statistically significantly different from the main analyses in terms of either cumulative uptake (S-Table-5 in Supplementary Material) or dose completion (S-Table-6 in Supplementary Material). In the sensitivity analyses for the subsidised and school-based vaccination within the counties that were included in the analysis of catch-up outside-school vaccination, results were likewise similar (S-Table-7 in Supplementary Material). The cumulative uptake of the vaccine in catch-up vaccination administrated in schools was similarly high as the uptake in school-based vaccination, and the adjusted hazard ratios in relation to parental COB and level of education was also close to those in school-based vaccination (S-Figure-2, S-Table-8 in Supplementary Material). In our analysis of uptake by specific region of origin for parents, results were not completely stable across vaccination deliveries (S-Table-9 in Supplementary Material).

4. Discussion

4.1. Main findings and interpretations

In this nationwide cohort study, we found that in subsidised opportunistic vaccination, the uptake of HPV vaccination was limited and slow, and strongly associated with parents' country of birth (COB) and socioeconomic characteristics. In free-of-charge catch-up outside-school vaccination, uptake was quicker, and disparities slightly less pronounced. In free-of-charge school-based vaccination, high uptake of the vaccine was achieved in short time, and disparities in terms of COB and socioeconomic characteristics were largely attenuated.

In the first assessment of uptake in the Swedish subsidised vaccination, it was found that girls with parents of high education level were 15-fold more likely to be vaccinated than those with parents of low education level (Leval et al., 2013). This disparity is nowadays largely removed among the girls vaccinated in school-based vaccination. Our results suggest that mode of delivery of the vaccination is strongly associated with disparities in uptake. We observed a higher cumulative uptake and less signs of disparity in free of charge catch-up vaccination as compared to subsidised delivery, and the higher uptake was mainly observed among foreign-born, lower education and income groups (Fig. 4), which implies that completely eliminating vaccine cost may improve uptake among girls from foreign-born parents and families of lower socioeconomic status. The results that the cumulative uptake was higher in the school-based vaccination across all COB, education and income groups compared to those in the catch-up outside-school vaccination indicates that administration in school, which offers easy access and efficient information delivery, may lower barriers to vaccination across different groups in society, and potentially reduce disparities.

We note that age-at-vaccination is also a systematic difference between school-based and catch-up outside-school vaccination, as the

Table 2
HPV vaccine uptake and completion by vaccination delivery mode among girls eligible for HPV vaccination in Sweden during 2007–2014.

Vaccination delivery mode	No. of girls	Mean follow-up time (month)	No. of vaccinated with the first dose	Cumulative uptake %[a]	3-dose completion[b]
Subsidised opportunistic	480,906	28.7	103,260	37.3	89.4
Free catch-up outside-school	45,532	17.9	17,558	47.8	66.0
Free school-based	207,467	12.4	136,823	79.2	81.8

[a] By 2014-12-31, calculated as the cumulative incidence proportion of vaccine initiation.
[b] Only calculated among those vaccinated with the first dose before July 1, 2014, to yield sufficient study time to allow completion of schedule according to dose interval recommendation.

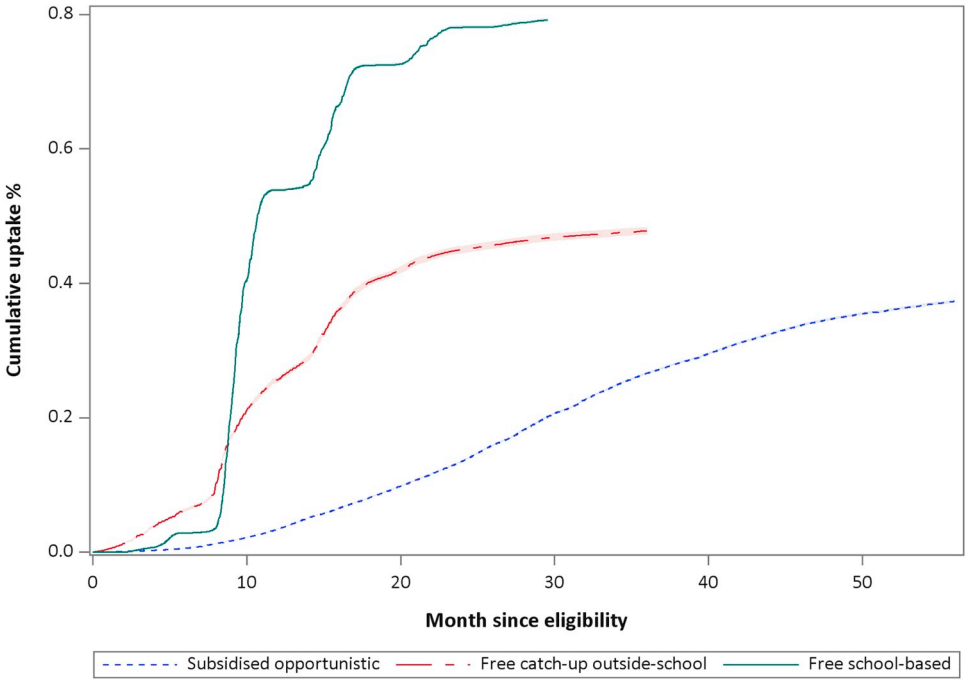

Fig. 3. Cumulative uptake of HPV vaccine by delivery mode of vaccination, as a function of month since being eligible for each delivery mode.

school-based vaccination targets girls aged around 10–12 years, while the catch-up vaccination covers the ages of around 13–18 years. However, age-at-vaccination may be less prominent than administration setting in terms of driving the associations of focus, given our supplementary results that the uptake and COB/socioeconomic differences in the two counties administrating catch-up vaccination in schools were similar to the school-based vaccination, although this comparison should be interpreted with some caution since the results were derived from two counties only. Although calendar period effects may play a role in the difference between subsidised vaccination and the other two modes of delivery, the difference between school-based and catch-up vaccination cannot have been arisen from such since they were implemented during the same calendar period. Also, we note that introducing the HPV vaccine to the National Immunisation Programme may also promote uptake in school-based vaccinations, due to the resulting signals of trust in the vaccine emanating from authorities, and more active encouragement from the organiser. Our findings are in agreement with a Belgian study showing high coverage and low disparity regarding family income in school-based, free HPV vaccination as compared to the non-school-based, co-payment mode (Lefevere et al., 2015). They also align with a Canadian study which found girls in deprived neighbourhoods were more likely to be HPV-vaccinated in "school delivery" compared to "community delivery" (Musto et al., 2013).

Although in school-based vaccination, uptake is relatively high and disparity largely attenuated, the uptake is still below the level of other childhood vaccines in Sweden (World Health Organisation, n.d.), and residual COB and socioeconomic differences remain. This emphasises the need to target lower uptake groups for further improving vaccination coverage, and reduce the risk of later inequalities in cervical cancer incidence, especially considering the evidence that the unvaccinated group tends to also participate less in cervical screening (Herweijer et al., 2015). Girls with foreign-born parents were 18% less likely to be HPV vaccinated compared to those with Swedish-born parents, a difference not explained by differing education or income. Further analysis revealed that girls of mothers from certain regions had lower HPV vaccine uptake. The pattern in school-based vaccination delivery was similar to recent findings in the neighbouring country of Norway (Hansen et al., 2015). It is possible that the lower uptake may be due to a language barrier, and also partially be explained by e.g. cultural differences, uptake of health services in general and the attitude to HPV vaccine in their country of origin. Low family income was independently associated with lower vaccine uptake even in the free-of-charge school-based vaccination programme. This has been found previously in other settings implementing similar school-based HPV vaccination programmes (Feiring et al., 2015; Slåttelid Schreiber et al., 2015). This may indicate that there are other characteristics related to low family income that are associated with the vaccine uptake apart from financial issues, COB background, and education. Norwegian and Canadian studies have shown that in free-of-charge school-based HPV vaccination programmes, high maternal education was significantly associated with lower probability of initiating HPV vaccination (Feiring et al., 2015; Hansen et al., 2015; Ogilvie et al., 2010). A possible reason is that more highly educated parents may be relatively more cautious when facing a newly introduced vaccine (Dahlström et al., 2010; Marlow et al., 2007). However, we found in the present study that parental education was actually positively associated with vaccine uptake regardless of delivery mode of the vaccine, and other studies have reported similar results regarding education (Polonijo and Carpiano, 2013; Slåttelid Schreiber et al., 2015). Further investigation on how to close the gap in uptake between HPV vaccines and other pediatric vaccines is also warranted.

We found that dose completion was relatively high in the subsidised opportunistic and school-based vaccination, but low in the catch-up outside-school delivery. As individuals participating in the subsidised programme typically paid the full price for the first dose and got remaining two doses almost for free according to the subsidy execution, this may indicate that they were more motivated to complete the full course of vaccination. In free-of-charge catch-up vaccination administrated outside of schools, on the other hand, girls and parents may have been economically less motivated to complete the doses, and the out-of-school administration may likely have made completion less convenient. In the free school-based vaccination, although economic incentives to complete schedules were lacking, school administration did offer easy access which may likely have increased chances of completion. Dose completion was only weakly associated with the here

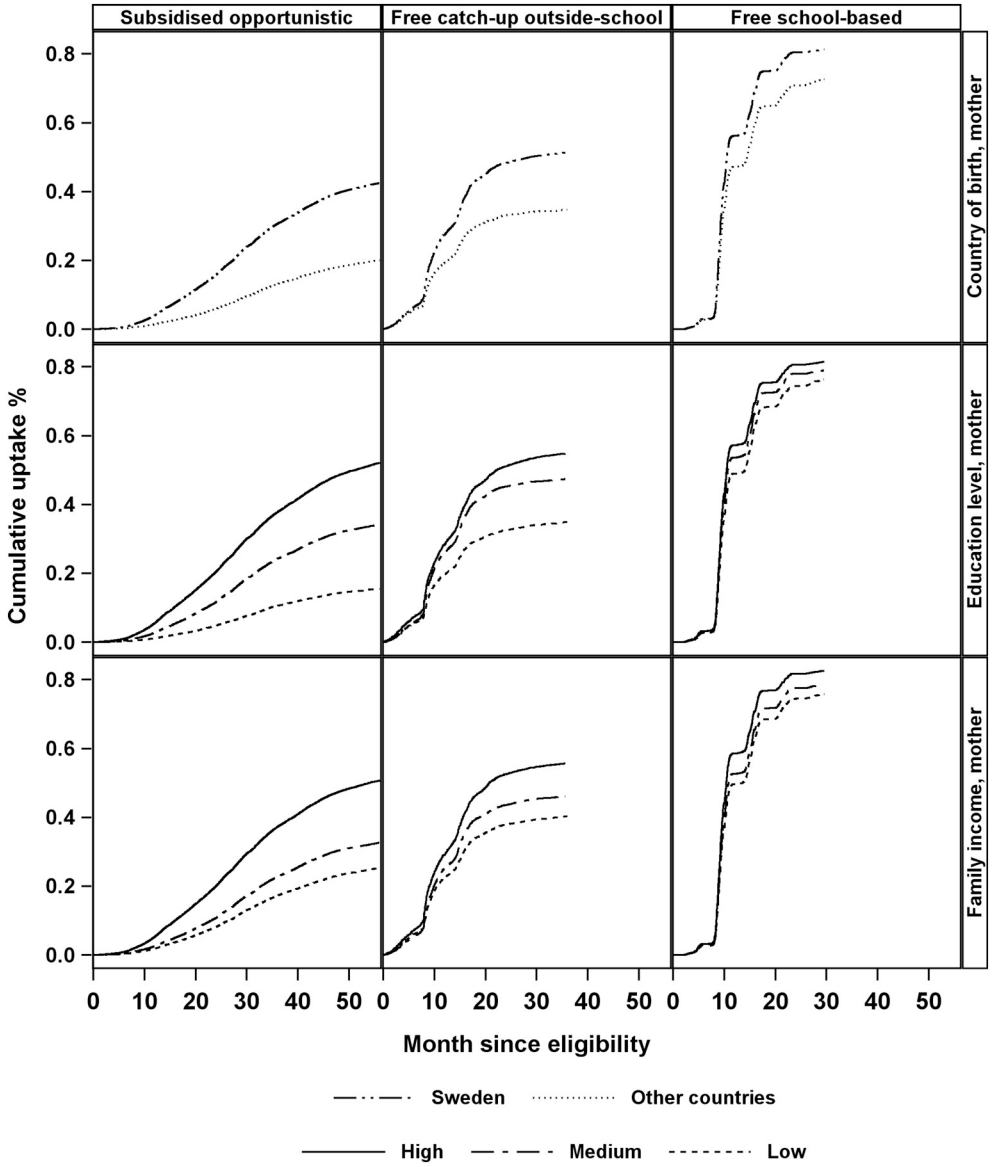

Fig. 4. Cumulative uptake of HPV vaccine by maternal characteristics and vaccination delivery mode.

Table 3
Relative uptake[a] of HPV vaccine associated with maternal characteristics, by vaccination delivery mode, among girls eligible for HPV vaccination in Sweden during 2007–2014.

	Crude hazard ratio (95% confidence interval)			Adjusted hazard ratio (95% confidence interval)[b]		
	Subsidised opportunistic	Free catch-up outside-school	Free school-based	Subsidised opportunistic	Free catch-up outside-school	Free school-based
Country of birth[c]						
Sweden	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Other countries	0.38(0.38–0.39)	0.63(0.60–0.65)	0.77(0.76–0.78)	0.49(0.48–0.50)	0.69(0.66–0.72)	0.82(0.81–0.83)
Education level[c]						
High	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	0.57(0.56–0.57)	0.85(0.82–0.88)	0.91(0.90–0.93)	0.63(0.62–0.63)	0.88(0.85–0.91)	0.95(0.94–0.96)
Low	0.23(0.22–0.23)	0.59(0.56–0.62)	0.81(0.79–0.82)	0.32(0.31–0.33)	0.70(0.66–0.74)	0.92(0.91–0.94)
Family income[c]						
High	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	0.55(0.54–0.55)	0.79(0.76–0.82)	0.86(0.85–0.87)	0.67(0.66–0.68)	0.87(0.84–0.90)	0.92(0.91–0.94)
Low	0.40(0.39–0.41)	0.67(0.64–0.69)	0.79(0.78–0.80)	0.53(0.52–0.54)	0.78(0.75–0.81)	0.87(0.85–0.88)

[a] Number of girls and number of girls vaccinated in each category is presented in S-Table-1 in Supplementary Material.
[b] Adjusted for county of residence, and the other two factors.
[c] Category of missing is included in the models, but not presented.

Table 4
Relative dose completion[a] associated with maternal characteristics, by vaccination delivery mode, among girls vaccinated with the first dose of HPV vaccination before July 1, 2014, in Sweden during 2007–2014.

	Crude odds ratio (95%CI)			Adjusted odds ratio (95%CI)[b]		
	Subsidised opportunistic	Free catch-up outside-school	Free school-based	Subsidised opportunistic	Free catch-up outside-school	Free school-based
Country of birth[c]						
Sweden	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Other countries	0.81(0.76–0.87)	0.70(0.64–0.76)	0.83(0.80–0.86)	0.89(0.83–0.95)	0.77(0.71–0.85)	0.89(0.85–0.92)
Education level[c]						
High	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	1.16(1.11–1.20)	1.00(0.93–1.07)	0.99(0.95–1.02)	1.16(1.11–1.21)	1.00(0.93–1.07)	0.99(0.96–1.03)
Low	0.87(0.80–0.96)	0.72(0.65–0.80)	0.85(0.81–0.89)	0.93(0.85–1.03)	0.80(0.72–0.90)	0.93(0.88–0.98)
Family income[c]						
High	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	1.03(0.99–1.08)	0.99(0.92–1.07)	0.98(0.95–1.02)	0.99(0.94–1.03)	1.03(0.96–1.11)	0.98(0.94–1.02)
Low	0.81(0.76–0.86)	0.81(0.74–0.87)	0.86(0.82–0.89)	0.78(0.74–0.83)	0.87(0.80–0.95)	0.88(0.84–0.92)

[a] Number of girls vaccinated and proportion of dose schedule completion is presented in S-Table-2 in Supplementary Material.
[b] Adjusted for county of residence, and the other two factors.
[c] Category of missing is included in the models, but not presented.

studied COB and socioeconomic factors, which may be due to that the vaccinated group is already positively selected towards vaccination.

4.2. Strengths and limitations

The national registers of HPV vaccination provided extensive and detailed information needed in our study. Individual linkage to national registers with high-quality demographic and socioeconomic data enabled individual-level analyses, prevented potential recall- or reporting bias, and allowed multidimensional assessment of socioeconomic characteristics. By using a cohort approach, we could longitudinally and explicitly categorize the vaccination deliveries that each girl had been eligible for, and show not only the differences in overall uptake, but also time to receiving the vaccine between vaccination deliveries. We furthermore retrieved parents' education and family income the year before their daughters being eligible for each certain vaccination delivery, which allowed for some social mobility to be considered among the participants. In total, this meant that we could perform the most comprehensive evaluation across mode of delivery of HPV vaccination done so far (Lefevere et al., 2015; Paul and Fabio, 2014).

In terms of limitations, this being an observational study, we cannot infer causality in the association between delivery modes of the vaccine and overall uptake with reduced disparities. Still, our study may be compared to a natural experiment, since the three delivery modes were assessed within one country which enhances similarity between groups. Moreover, anonymous vaccinations, i.e. vaccination records that could not be linked to any individual, resulted in a degree of underestimation of vaccination uptake in our data. It was not possible to assess potential differences in socioeconomic status between anonymous and identified vaccinations, thus we were unable to directly assess whether our estimates of COB/socioeconomic differences were generalisable to the anonymous group. However, in sensitivity analyses restricted to girls living in counties with anonymous vaccinations of less than 15%, our estimates did not change notably. There may be interactions between COB and socioeconomic factors that we have not explored, since this was not a primary interest of the present study. Rather, the reported association estimated from multivariable models was aimed to represent the direct and independent statistical effect measure of each factor on vaccine uptake. Finally, around 2–6% of parents had no information on country of birth, education or family income in the registries. A large proportion of those missing education and family income were foreign-born, or had missing data on country of birth (S-Table-10 in Supplementary Material), and the missing categories were generally associated with lower vaccine uptake (S-Figure-3 in Supplementary Material). These missing categories were included in the statistical models. Since missing data generally represented a small fraction of the studied population it is not likely that this had relevant impact on the estimates.

5. Conclusion

School-based, free-of-charge HPV vaccination appears the most effective strategy for reaching whole populations in an equitable manner. Further efforts should be put towards improving vaccination uptake among girls with foreign-born parents and low family income, who may still be at risk of not fully benefitting of the offer of vaccination.

Acknowledgements

The authors thank Pouran Almstedt for data management.

Funding

This work was supported by Swedish Foundation for Strategic Research [grant number KF10-0046]; The Swedish Cancer Society [grant number 160699]; The Swedish Research Council [grant number 2017-02346]; and Nordforsk [grant number 62721].

Ethical approval

All procedures performed in the study involving human participants were in accordance with the ethical approval for this study granted by the Regional Ethics Committee in Stockholm, Sweden.

Informed consent

Informed consent from the study subjects was not required according to the ethical approval, since the identity of subjects in the study population is unknown to researchers and readers.

Competing interest

LAD has received grants from Merck & CO. for study on other vaccines than Gardasil. KS has received grants from Merck & CO. for other studies on HPV vaccination in Sweden. Other authors declare that no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

All relevant source data are shown in the manuscript and supplementary files. If access to raw data is required, please contact par.sparen@ki.se. Data may be shared if all ethical and legal requirements are met for such a request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.12.014.

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