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Adverse pregnancy outcomes and infant mortality after quadrivalent HPV vaccination during pregnancy

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ABSTRACT

Background: Few studies have studied the association between unintended human papillomavirus (HPV) vaccination and adverse pregnancy outcomes. This study set out to determine the association between HPV vaccination during pregnancy and subsequent risk of spontaneous abortion, stillbirth, and one-year infant mortality.

Methods: Population-based study including all pregnancies in Denmark (October 2006–December 2014) among women born 1975–1992. From nationwide health registries using the personal identification numbers, we obtained information on HPV vaccination, pregnancy outcomes, and infant mortality. The exposure window went from four weeks before conception date until 22 weeks of gestation for the outcome spontaneous abortion, and until birth for stillbirth and infant mortality outcomes. In the analyses of spontaneous abortion, we used time to event models, for stillbirth logistic regression models, and for infant mortality Cox regression was applied.

Results: We included 522,705 pregnancies for the outcome spontaneous abortion (7487 exposed to at least one dose during pregnancy); 351,878 births (5262 exposed to at least one dose during pregnancy) for the stillbirth; and 350,739 live births (5245 exposed to at least one dose during pregnancy) for infant mortality. No significantly increased rate of spontaneous abortion among women vaccinated during pregnancy compared with unvaccinated women was found. In addition, we found no association between HPV vaccination during pregnancy and stillbirth (adjusted odds ratio = 0.96 [95% CI: 0.57–1.61]), or infant mortality (adjusted hazard ratio = 0.94 [95% CI: 0.53–1.67]). A secondary analysis showed no association between number of doses and timing of administration (i.e. vaccination before or during pregnancy) and an increased risk of spontaneous abortion.

Conclusion: We found no increased risk of spontaneous abortion, stillbirth, or infant mortality following unintended HPV vaccination during pregnancy.

1. Introduction

Persistent infection with human papillomavirus (HPV) is the major etiological risk factor for cervical cancer. HPV is also associated with other anogenital cancers as well as a subset of oropharyngeal cancers [1]. In October 2006, a quadrivalent vaccine containing virus-like particles of HPV types 6, 11, 16, and 18 was licensed in Denmark. It was included in the free of charge childhood vaccination program in January 2009 covering 12 year old girls, and in catch-up programs for respectively girls 13–15 years (initiated in October 2008) and women up to age 27 years (initiated in August 2012).

Vaccination of women of reproductive age makes it possible that unintended vaccination during pregnancy (i.e. vaccination of women before they knew they were pregnant) can occur. Only two studies have examined the association between vaccination with the quadrivalent HPV vaccine during pregnancy and risk of adverse pregnancy outcomes [2,3]. However, these studies had some limitations such as a relatively low number of events, loss to follow-up, being based on voluntary reporting, or lack of adjustment for potentially confounding factors. Moreover, the

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association between HPV vaccination during pregnancy and subsequent infant mortality has not previously been investigated.

This prompted us to examine the association between HPV vaccination during pregnancy and the subsequent risk of outcomes that may occur in the continuum from conception to birth and into infant life, including spontaneous abortion, stillbirth, and one-year infant mortality. We were able to take into account different aspects of vaccination including number of doses and exposure window in relation to conception as well as several potentially confounding factors.

2. Materials and methods

In Denmark, all residents are assigned a unique personal identification number (PIN) comprising information on sex and date of birth. The PINs are registered in the Danish Civil Registration System and are used as identifiers in all national registers, allowing accurate linkage between registers [4].

The study was approved by the Danish Data Protection Agency (journal no. 2015-41-4461).

2.1. Study population

The study population consisted of all births and all pregnancies not resulting in birth (spontaneous abortions, induced abortions, molar and ectopic pregnancies, and other pregnancy outcomes) in Denmark ending from October 1, 2006 to December 31, 2014 among women born 1975–1992. These data were obtained from The Medical Birth Registry [5], which includes information on all deliveries with infants showing signs of life and all stillbirths since 1973, and the National Patient Registry [6], which contains data on virtually all hospitalizations for somatic conditions in Denmark since 1977. Among women born after 1992, only few pregnancies were registered and a limited number of these resulted in a spontaneous abortion. Furthermore, a considerable proportion (more than 50%) of the pregnancies ended as an induced abortion, which is a competing event to spontaneous abortion. Therefore, women born later than 1992 were excluded from our analyses.

2.2. Exposure

Information on HPV vaccination and dates of vaccination or purchase of the vaccine was obtained from the Health Service Registry and the Danish Prescription Registry. The Health Service Registry holds data since 1990 on the activities of primary healthcare professionals paid by the public healthcare systems [7]. Using the service codes for HPV vaccination (8328, 8329, 8330, 8334, 8335, and 8336) we identified girls and women who had received HPV vaccination within the free of charge vaccination program from October 2008 up to 2014. The Danish Prescription Registry holds information on all prescription drugs sold in Danish community pharmacies since 1995 [8]. From this register, we identified girls and women who purchased an HPV vaccine on prescription since licensure of the HPV quadrivalent vaccine in October 2006 by extracting the Anatomical Therapeutic Chemical categories J07BM01 (quadrivalent vaccine) and J07BM02 (bivalent vaccine).

For the analyses of spontaneous abortion, the exposure window for all pregnancies was defined as four weeks before conception date until 22 weeks of gestation or date of abortion, whichever came first. For the analyses of stillbirth and one-year infant mortality, the exposure window was defined as four weeks before conception date until birth. The exposure was defined as at least one dose within the exposure window. Women with vaccinations both prior to pregnancy (i.e. >four weeks before conception date) and during pregnancy were classified as vaccinated during pregnancy.

2.3. Outcomes

Spontaneous abortion was defined as spontaneous fetal loss within 22 weeks of gestation using the following International Classification of Diseases, 10th edition (ICD10) codes: O03, O02.0, O02.1 and O02.9. In Denmark, women have a legal right to induced abortion within 12 weeks of gestation. The following ICD10-codes for induced abortions were used: O04-O06. Molar and extra uterine pregnancies were covered by the ICD-10 codes O00 and O01, and the ICD-10 codes O02.2 and O02.8 covered other pregnancy outcomes ('termination of pregnancy with unknown localization' and 'other specified abnormal products of conception'). A stillbirth may occur from 23 weeks of gestation until term and was defined as the birth of a dead fetus or the birth of a fetus dying during delivery. Infant mortality was defined as the death of an infant within its first year of life.

2.4. Information on potential confounders

We obtained information about birth year of the women, age at conception, and ethnicity from the Civil Registration System, education and marital status from registries in Statistics Denmark, number of previous births, body mass index (BMI), and smoking status from the Medical Birth Registry, and number of induced and spontaneous abortions from the National Patient Registry. Finally, we collected information on history of genital warts, chlamydia, and pelvic inflammatory disease (PID) from the National Patient Registry. Information on history of genital warts was also collected from the Danish Prescription Registry.

2.5. Statistical analysis

To evaluate the association between spontaneous abortion and unintended HPV vaccination during pregnancy we performed a grouped time-to-event analysis with gestational period as underlying time scale. End of follow-up was defined as either time of spontaneous abortion, induced abortion or end of gestational week 22 whichever occurred first. Exposure status (at least one dose within the exposure window) was included as a time-varying variable (yes/no). The gestational time period was divided into eight periods (gestational week < 7, 7, 8, 9, 10, 11, 12, and gestational weeks 13–22) and for each period a rate ratio (RR) for spontaneous abortion was estimated [9], i.e. for vaccinated vs. unvaccinated. To examine the influence of the competing event induced abortion, subdistribution RRs were estimated ignoring induced abortions [10]. The associations between unintended HPV vaccination during pregnancy and risk of stillbirth was estimated using logistic regression. For infant mortality, a Cox proportional hazards model was applied. Both age-adjusted and fully adjusted estimates with 95% confidence intervals (CI) were computed. The full adjustment for spontaneous abortion included the following a priori selected variables related to the woman: age at conception, birth year, education, marital status, ethnicity, number of previous births, number of previous spontaneous abortions, number of previous induced abortions, and history of genital warts, chlamydia, and PID. In the analyses of stillbirth and infant mortality, we adjusted for the following a priori selected variables related to the woman: age at conception, education, BMI, and smoking. Age at conception and BMI were included as restricted cubic splines. The main analyses were performed on complete cases (i.e. pregnancies with no missing information on the covariates included in the multivariable models) and with pregnancies among women who had never been vaccinated as reference group.

For the outcome spontaneous abortion, we also estimated the risk assuming a constant effect of vaccination during pregnancy by logistic regression. For this analysis, two additional analyses

were conducted. First, we divided the exposure according to the number of vaccine doses administered during pregnancy (i.e. from four weeks prior to conception until 22 weeks of gestation) only, or both during and prior (i.e. >four weeks before conception date) to pregnancy. Second, the risk of spontaneous abortion was examined for women vaccinated during the four weeks prior to conception and women vaccinated after conception separately.

For the outcomes stillbirth and infant mortality, the analyses were repeated on all available births using multiple imputation assuming that covariate information was missing at random. The missing covariates were imputed from outcome information, age at conception, education, marital status, ethnicity, number of previous births, smoking status, BMI, birth year of the woman, and vaccination status. The estimates were obtained with the substantive model compatible fully conditional specification method with five imputations for each outcome [11].

To examine whether the conclusions for all three outcomes were different for women who were offered the vaccine free of charge, a sensitivity analysis among women born 1985–1992 was performed with same strategy as in the main analyses. Further, to evaluate differences between unvaccinated and vaccinated women, the main analyses were repeated with pregnancies among women vaccinated prior to the exposure window as the unexposed reference group.

The proportional hazard assumption was tested for the Cox models with no apparent evidence of violations.

All analyses were conducted using the statistical software R, version 3.2.3 with packages [12,13].

3. Results

A total of 534,377 unique pregnancies were identified in the study period among women born 1975–1992. Some pregnancies were not properly classified as either spontaneous or induced abortions and these were excluded from the analyses (n = 2482). Pregnancies with no information on gestational age (n = 9068) or without information on the PIN of the child were excluded (n = 5). As the quadrivalent vaccine was used in the Danish HPV vaccination program until December 31, 2015 and only a limited number of women purchased the bivalent HPV vaccine in the study period, women vaccinated with the bivalent vaccine before or during pregnancy were excluded from the analyses (n = 117). Analyses on spontaneous abortion were based on all included pregnancies (n = 522,705). Of these, 390,673 were births (382,911 singleton and 7762 non-singleton births) and 132,042 were abortions (49,265 spontaneous and 78,055 induced abortions) and other pregnancies (n = 4712) ending before week 22 of gestation (Fig. 1). For the outcomes stillbirth and infant mortality non-singleton births were excluded (n = 7762). Analyses on these two outcomes were based on births with conception date no earlier than October 28, 2006 corresponding to 4 weeks after licensure of the quadrivalent vaccine in Denmark to allow exposure to HPV vaccination (n = 351,878) (Fig. 2).

For the outcome spontaneous abortion, 522,705 unique pregnancies ending in the period from October 1, 2006 to December 31, 2014 among women born 1975–1992 met the inclusion criteria. Of these, 479,298 were among unvaccinated women, 35,920 pregnancies were among women vaccinated prior to pregnancy only (i.e. >four weeks before conception date) and 7487 pregnancies were among women exposed to at least one dose during pregnancy (i.e. four weeks prior to conception until 22 weeks of gestation) (Fig. 1). For the outcome stillbirth we included 351,878 births (322,243 births among unvaccinated women, 24,373 births among women vaccinated prior pregnancy only, and 5262 births among women receiving at least one dose during pregnancy). For infant mortality we included 350,739 live births (321,198 live births among unvaccinated women, 24,296 live births among women vaccinated prior to pregnancy only, and 5245 live births among women who had at least one dose during pregnancy) (Fig. 2).

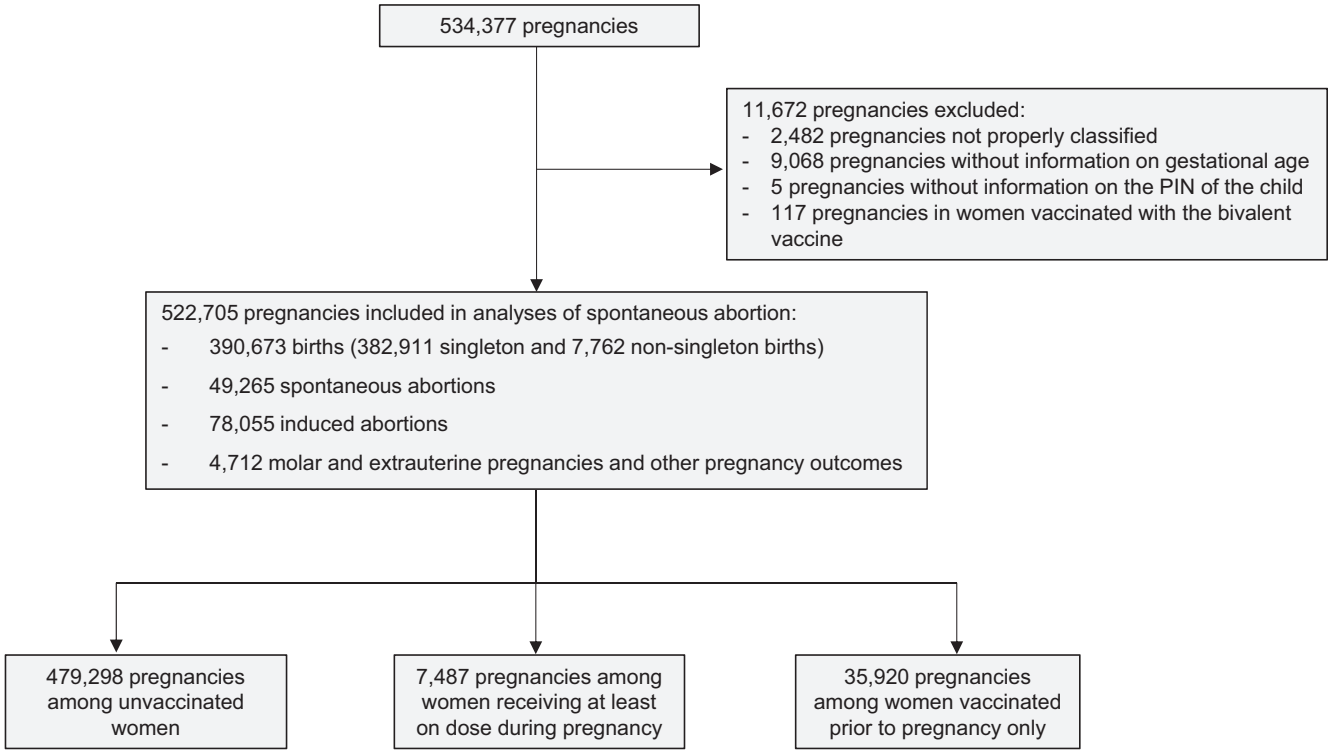

Fig. 1. Flow diagram of inclusions and exclusions for the outcome spontaneous abortion.

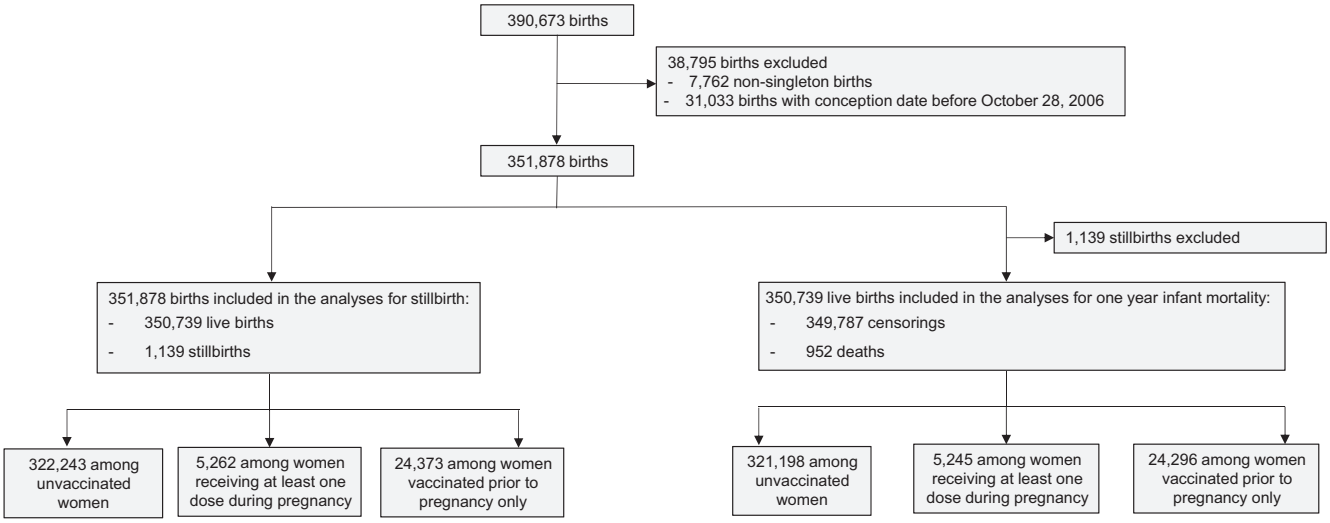

Fig. 2. Flow diagram of inclusions and exclusions for the outcomes stillbirth and infant mortality.

Tables 1 and 2 present characteristics for unexposed (unvaccinated) and exposed pregnancies (vaccinated during pregnancy) for the outcome spontaneous abortion and the outcomes stillbirth and infant mortality, respectively. For all three outcomes, the average age at conception was higher among unexposed than among exposed. The median gestational age at time of spontaneous abortion was similar for unexposed and exposed pregnancies. For stillbirths, the median gestational age was higher among unexposed than exposed pregnancies, while for infants surviving <1 year it was lower among unexposed than exposed, although the interquartile ranges were wide. For all three outcomes, the educational level was generally higher in unexposed than in exposed women, more unexposed than exposed women were married, and the frequency of immigrants and number of previous births was higher among unexposed than exposed women (Tables 1 and 2). The proportion of previous spontaneous abortions was slightly higher in unexposed than in exposed women, while the proportion of previous induced abortions was slightly higher in exposed women. A higher proportion of exposed than unexposed women had a history of genital warts and chlamydia (Table 1). Among births included in the analyses on stillbirth and infant mortality, a higher proportion of exposed than unexposed women were smokers, but smoking cessation during the first trimester was also more common among exposed than unexposed women. Obesity was somewhat more frequent in exposed than unexposed women (Table 2).

The results presented in Tables 3 and 4 are based on analyses performed on complete cases using unvaccinated women as unexposed reference group. Table 3 shows the association between HPV vaccination during pregnancy and the rate of spontaneous abortion for eight gestational periods among women born 1975–1992. The proportion of spontaneous abortions ranges from 1.1% to 1.6% among unexposed pregnancies and from 0.8% to 1.8% among exposed pregnancies. No significantly increased rate was found for any of the gestational periods after full adjustment. Accounting for competing events showed similar results (Supplementary 1).

For spontaneous abortions, we were able to investigate the potential effect of number of doses. This analysis showed that there was no substantial difference in the risk according to number of doses administered prior to or during pregnancy (Supplementary 2). An additional analysis for spontaneous abortions examining timing of vaccination showed that women vaccinated after conception (up to 22 weeks of gestation) did not have an increased risk of spontaneous abortion compared to women vaccinated in the period from four weeks before conception to date of conception (adjusted odds ratio (aOR) = 0.87; 95% CI: 0.74–1.04).

Table 4 shows the association between HPV vaccination during pregnancy and the subsequent risk of stillbirth and one-year infant mortality, respectively. In the complete case analysis, we observed 15 stillbirths and 12 cases of infant mortality among exposed women and the proportion of stillbirths and deaths in the first year of life was almost equal among unexposed and exposed pregnancies. No increased risk of either stillbirth (aOR = 0.96; 95% CI: 0.57–1.61) or infant mortality (adjusted hazard ratio = 0.94; 95% CI: 0.53–1.67) was observed after adjustment for potentially confounding factors. Analyses including the total study population with multiple imputation gave similar results (Supplementary 3)

In a sensitivity analysis among women born 1985–1992, where most vaccinated women were vaccinated as part of the free of charge vaccination program (97.6%), the main results for all three outcomes remained virtually unchanged (Supplementary 4). Analyses with pregnancies among women vaccinated only prior to pregnancy as the unexposed reference group showed a similar pattern (Supplementary 5).

4. Discussion

In this large, population-based study we found no increased risk of adverse pregnancy outcomes that may occur in the continuum from conception to birth and into infant life, including spontaneous abortion, stillbirth, and one-year infant mortality, following unintended HPV vaccination during pregnancy. In addition, the risk of spontaneous abortion was virtually identical among women vaccinated four weeks before conception and women vaccinated after conception, and there was no apparent effect of the number of vaccine doses administered during pregnancy.

Our study is in line with the findings in the two previous studies that investigated risk of spontaneous abortion following vaccination with the quadrivalent HPV vaccine during pregnancy [2,3]. In addition, we analyzed the effect of number of HPV vaccine doses for the risk of spontaneous abortion and thereby add valuable information to the existing knowledge. The present study is the largest to date, providing statistical power to obtain reassuring results in relation to risk of still birth following HPV vaccination during pregnancy. Furthermore, to our knowledge, the present study is the first to examine the association between HPV vaccina-

Table 1
Characteristics of unexposed (unvaccinated) and exposed (vaccinated during pregnancy) pregnancies for the outcome spontaneous abortion.

	Not vaccinated (unexposed) (N = 479,298)	Vaccinated during pregnancy (exposed) (N = 7487)
(No. of complete cases)	(466,152)	(7441)
Age at conception (years)	28.5 (4.4)	25.5 (3.2)
Mean (SD)		
Gestational age for spontaneous abortions (weeks)	8.9 (7.0–11.0)	8.9 (7.0–11.)
Median (IQR)		
	No. of pregnancies (%)	No. of pregnancies (%)
Education		
Primary (7–10 y)	112,727 (23.5)	2,490 (33.3)
High school/vocational (10–12 y)	168,884 (35.2)	3,254(43.5)
Higher (≥13 y)	161,410 (33.7)	1,426(19.0)
Unknown	35,490 (7.4)	<400(<5.0)[a]
Missing	787 (0.2)	<5 (<0.1)[a]
Marital status		
Single	298,272 (62.2)	6119 (81.7)
Married/cohabiting	154,944 (32.3)	1232 (16.5)
Divorced	12,659 (2.6)	88 (1.2)
Widowed	277 (0.1)	<5 (<0.1)[a]
Missing	13,1446 (2.7)	<50 (<0.7)[a]
Ethnicity		
Danish	394,289 (82.3)	6659 (88.9)
Immigrant	73,439 (15.3)	603 (8.1)
Descendant of immigrant	11,451 (2.4)	225 (3.0)
Missing	119 (<0.1)	0 (0.0)
Number of previous births		
None	238,828 (49.8)	4575 (61.1)
1	164,872 (34.4)	2240 (29.9)
2	58,649 (12.2)	570 (7.6)
>2	16,949 (3.5)	102 (1.4)
Number of previous spontaneous abortions		
None	406,311 (84.8)	6696 (89.4)
1	60,820 (12.7)	680 (9.1)
2	9867 (2.1)	91 (1.2)
>2	2300 (0.5)	20 (0.3)
Number of previous induced abortions		
None	388,163 (81.0)	5856 (78.2)
1	63,611 (13.3)	1140 (15.2)
2	17,403 (3.6)	315 (4.2)
>2	10,121 (2.1)	176 (2.4)
History of genital warts		
Yes	13,933 (2.9)	313 (4.2)
No	465,365 (97.1)	7174 (95.8)
History of chlamydia		
Yes	2063 (0.4)	44 (0.6)
No	477,235 (99.6)	7443 (99.4)
History of PID		
Yes	14,471 (3.0)	169 (2.3)
No	464,827 (97.0)	7318 (97.7)

Abbreviations: SD = Standard deviation; IQR = Interquartile range.
[a] Due to small numbers in these categories the exact numbers are not shown according to regulations.

tion during pregnancy and risk of infant mortality, and also for this outcome no increased risk was associated with vaccination during pregnancy, however the latter result was based on a limited number of outcomes. Our results are reassuring and add to the favorable safety profile of HPV vaccination.

Our study is the first to examine the effect of number of doses of the quadrivalent HPV vaccine given during pregnancy. Our finding that the risk of spontaneous abortion is not affected by number of vaccine doses administered is in line with some studies that investigated the effect of number of doses of the bivalent vaccine [14,15]. By contrast, Baril et al. [16], reported that women who received two doses of the bivalent HPV vaccine within 45 days before to 30 days after first day of gestation had an increased risk of spontaneous abortion compared with unexposed women.

The main strengths of our study are that it covers all pregnancies and births in Denmark in the birth cohorts 1975–1992 during the study period and that we identified virtually all girls and women vaccinated against HPV types 6, 11, 16, and 18, resulting in adequate statistical power. The collection of information on exposure as well as outcome from high-quality nationwide registers virtually excludes the risk of selection and recall bias. We were able to adjust for a variety of potentially confounding factors and we also included sensitivity analyses with imputation of data for variables with missing values. Further, we had virtually no loss to follow-up. Finally, the exposed population was compared to two different comparison groups, namely an unexposed population of never vaccinated and an unexposed population of women vaccinated prior to pregnancy only in order to eliminate confounding

Table 2
Characteristics of unexposed (unvaccinated) and exposed (vaccinated during pregnancy) pregnancies for the outcomes stillbirth and infant mortality.

	Stillbirth		Infant mortality (1st year)	
	Not vaccinated (unexposed) (N = 322243)	Vaccinated during pregnancy (exposed) (N = 5262)	Not vaccinated (unexposed) (N = 321,198)	Vaccinated during pregnancy (exposed) (N = 5245)
(No. of complete cases)	(309,010)	(5,160)	(308,062)	(5145)
Age at conception (years) *(Mean (SD))*	29.0 (4.1)	25.9 (3.0)	29.0 (4.1)	25.9 (3.0)
Gestational age for stillbirths and deaths <1 year (weeks) *(Median (IQR))*	31.9 (24.9–38.0)	25.4 (23.3–38.6)	32.4 (24.1–39.0)	37.2 (26.5–38.5)
	No. of pregnancies (%)	No. of pregnancies (%)	No. of pregnancies (%)	No. of pregnancies (%)
Education				
Primary (7–10 y)	57,898 (18.0)	1356 (25.8)	57,627 (17.9)	1351 (25.8)
High school/vocational (10–12 y)	115,062 (35.7)	2,455 (46.7)	114,732 (35.7)	2445 (46.6)
Higher (≥13 y)	124,730 (38.7)	1223 (23.2)	124,393 (38.7)	1221 (23.3)
Unknown	24,019 (7.5)	228 (4.3)	23,914 (7.4)	228 (4.3)
Missing	534 (0.2)	0 (0.0)	532 (0.2)	0 (0.0)
Marital status				
Single	190,609 (59.2)	4120 (78.3)	189,995 (59.2)	4087 (77.9)
Married/cohabiting	114,897 (35.7)	1068 (20.3)	114,538 (35.7)	1067 (20.3)
Divorced	7857 (2.4)	59 (1.1)	7823 (2.4)	58 (1.1)
Widowed	177 (0.1)	<5 (<0.1)[a]	176 (0.1)	<5 (<0.1)[a]
Missing	8703 (2.7)	<50 (<1.0)[a]	8666 (2.7)	<50 (<1.0)[a]
Ethnicity				
Danish	265,018 (82.2)	4658 (88.5)	264,207 (82.3)	4,641 (88.5)
Immigrant	49,781 (15.4)	441 (8.4)	49,583 (15.4)	441 (8.4)
Descendant of immigrant	7411 (2.3)	163 (3.1)	7376 (2.3)	163 (3.1)
Missing	33 (0.0)	0 (0.0)	32 (<0.01)	0 (0.0)
Number of previous births				
None	157,241 (48.8)	3156 (60.0)	156,660 (48.8)	3,144 (59.9)
1	120,115 (37.3)	1740 (33.1)	119,833 (37.3)	1,738 (33.1)
2	35,909 (11.1)	313 (5.9)	35,789 (11.1)	310 (5.9)
>2	8978 (2.8)	53 (1.0)	8916 (2.8)	53 (1.0)
Smoking				
Non-smoker	276,123 (85.7)	4,390 (83.4)	275,310 (85.7)	4377 (83.5)
Stopped during 1st trimester	7731 (2.4)	194 (3.7)	7708 (2.4)	194 (3.7)
Stopped after 1st trimester	1740 (0.5)	38 (0.7)	1737 (0.5)	38 (0.7)
Current smoker	31,492 (9.8)	582 (11.1)	31,329 (9.8)	579 (11.0)
Unknown	5,157 (1.6)	58 (1.1)	5,114 (1.6)	57 (1.1)
BMI				
<18.5 kg/m^2 (underweight)	12,950 (4.0)	225 (4.3)	12,916 (4.0)	224 (4.3)
18.5–25.0 kg/m^2 (normal weight)	192,953 (59.9)	3,099 (58.9)	192,457 (59.9)	3,091 (58.9)
>25.0–30.0 kg/m^2 (overweight)	65,219 (20.2)	1114 (21.2)	64,981 (20.2)	1113 (21.2)
>30.0 kg/m^2 (obese)	38,371 (11.9)	722 (13.7)	38,218 (11.9)	717 (13.7)
Missing	12,750 (4.0)	102 (1.9)	12,626 (3.9)	100 (1.9)

Abbreviations: SD = Standard deviation; IQR = Interquartile range.
[a] Due to small numbers in these categories the exact numbers are not shown according to regulations.

Table 3
Rate ratios (RR) and 95% confidence intervals (CI) for the association between human papillomavirus vaccination during pregnancy and subsequent risk of spontaneous abortion among women born 1975–1992 in eight periods of gestation. Numbers and estimates are based on complete cases and with pregnancies among unvaccinated women as unexposed reference group.

Gestational period	No. of unexposed[a] pregnancies[b]	No. of unexposed[a] spontaneous abortions among (% of pregnancies)	No. of exposed[a] pregnancies[b]	No. of exposed[a] spontaneous abortions(% of pregnancies)	Age-adjusted RR	(95% CI)	Fully-adjusted RR[c]	(95% CI)
<week 7	466,883	5130 (1.1%)	6710	85 (1.3)	1.28	(1.03–1.58)	1.08	(0.87–1.34)
Week 7	453,456	6681 (1.5%)	6607	82 (1.2)	0.93	(0.75–1.16)	0.79	(0.63–0.98)
Week 8	433,063	6317 (1.5%)	6286	83 (1.3)	1.00	(0.81–1.24)	0.85	(0.68–1.05)
Week 9	410,974	6405 (1.6%)	5870	68 (1.2)	0.82	(0.65–1.04)	0.69	(0.54–0.88)
Week 10	391,860	4732 (1.2%)	5531	69 (1.2)	1.14	(0.90–1.45)	0.96	(0.76–1.22)
Week 11	379,241	4221 (1.1%)	5332	42 (0.8)	0.78	(0.58–1.06)	0.66	(0.48–0.89)
Week 12	369,376	4131 (1.1%)	5188	61 (1.2)	1.16	(0.90–1.50)	0.98	(0.76–1.26)
Week 13–22	360,701	5749 (1.6%)	5208	93 (1.8)	1.24	(1.01–1.52)	1.04	(0.85–1.28)

[a] Unexposed = Not vaccinated; Exposed = Vaccinated during pregnancy.
[b] Numbers vary for each period as all pregnancies are unexposed until the week of vaccination.
[c] Adjusted for age at conception, birth year of the woman, education, marital status, ethnicity, number of previous births, number of previous spontaneous and induced abortions, history of genital warts, chlamydia, and pelvic inflammatory disease.

Table 4
Distribution of births, stillbirths and deaths < 1 year after birth with odds ratios (OR) and hazard ratios (HR) and 95% confidence intervals (CI) for the association with human papillomavirus vaccination during pregnancy compared to unvaccinated among women born 1975–1992. Numbers and estimates are based on complete cases and with unvaccinated women as unexposed reference group.

Exposure status	No. of births	No. of stillbirths(% of births)	Age-adjusted OR	(95% CI)	Fully adjusted OR[a]	(95% CI)
Stillbirths						
Not vaccinated (unexposed)	309,010	948 (0.31)	1	Ref	1	Ref
Vaccinated during pregnancy (exposed)	5,160	15 (0.29)	0.93	(0.56–1.56)	0.96	(0.57–1.61)
	No. of births	No. of deaths < 1 year(% of births)	Age-adjusted HR	(95% CI)	Fully adjusted HR[a]	(95% CI)
Infant mortality (1st year)						
Not vaccinated (unexposed)	308,062	780 (0.25)	1	Ref	1	Ref
Vaccinated during pregnancy (exposed)	5,145	12 (0.23)	0.91	(0.51–1.61)	0.94	(0.53–1.67)

[a] Adjusted for age at conception, education, smoking, and BMI.

due to differences between vaccinated and unvaccinated women. Some limitations should also be mentioned. Among the vaccination program attenders we had information about the year and month, but not the exact date of HPV vaccination and among women who purchased the vaccine themselves we had information on the date of purchase, but not on the actual date that the women received the vaccine. However, considering that purchase of the vaccine is conditioned on prescription it is unlikely that the date of purchase and date of administration differ markedly. Furthermore, not all spontaneous abortions are registered in National Patient Registry as not all require medical attention. As the outcomes were based on coded data, the actual date of the fetal loss and the date of the medical visit for spontaneous abortion or stillbirth, may not be completely identical. Concerning the estimation of conception date, some abortions were registered with more than one gestational age with a median of 6 days between the dates. We used the date that resulted in the longest window of exposure. These uncertainties may slightly have influenced our results but most likely it is not substantially. Finally, as the induced abortions represent a competing risk for the spontaneous abortions, we cannot rule out that the true RRs of spontaneous abortions among the exposed women may slightly differ from the results in this study. However, the subdistribution analysis showed almost unchanged estimates indicating that the RRs of spontaneous abortion are not affected by the occurrence of induced abortions in the study population.

Given the nationwide, population-based design and the individual level data, this large, real-world study adds important information to the current knowledge. HPV vaccination is not recommended during pregnancy [17], but unintended exposure may occur. Therefore, the results from this and other studies are reassuring for women unintendedly vaccinated during pregnancy.

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Conflict of interest

Mette Tuxen Faber received travel grants from Sanofi Pasteur MSD. Christian Munk received lecture fees and travel grants from Sanofi Pasteur MSD. Susanne Krüger Kjaer received scientific advisory board fee from Merck, lectures fees from Merck and Sanofi Pasteur MSD, and unrestricted research grant through her institution from Merck. Anne Katrine Duun-Henriksen, Christian Dehlendorff, and Manrinder Kaur Tatla report no potential conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.030.

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