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Bivalent Vaccine Effectiveness Against Type-Specific HPV Positivity: Evidence for Cross-Protection Against Oncogenic Types Among Dutch STI Clinic Visitors

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Background. Observational postmarketing studies are important to assess vaccine effectiveness (VE). We estimated VE from the bivalent human papillomavirus (HPV) vaccine against HPV positivity of vaccine and nonvaccine types in a high-risk population.

Methods. We included all vaccine-eligible women from the PASSYON study, a biennial cross-sectional survey in Dutch sexually transmitted infection clinics. Vaginal swabs were analyzed using a polymerase chain reaction-based assay (SPF_{10}-$LiPA_{25}$) able to detect the 12 high-risk HPV (hrHPV) types 16/18/31/33/35/39/45/51/52/56/58/59. We compared hrHPV positivity between self-reported vaccinated (≥1 dose) and unvaccinated women, and estimated VE by a logistic mixed model.

Results. We included 1087 women of which 53% were hrHPV positive and 60% reported to be vaccinated. The adjusted pooled VE against HPV-16/18 was 89.9% (81.7%–94.4%). Moreover, we calculated significant VE against nonvaccine types HPV-45 (91%), HPV-35 (57%), HPV-31 (50%), and HPV-52 (37%). Among women who were offered vaccination 5/6 years ago, we estimated similar VE against HPV-16/18 (92%) and all hrHPV types (35%) compared to women who were offered vaccination <5 years ago (83% and 33%, respectively).

Conclusion. We demonstrated high VE of the bivalent vaccine against HPV-16/18 and cross-protection against HPV-45/35/31/52. Protection against HPV-16/18 was sustained up to 6 years postvaccination.

Keywords. human papillomavirus; human papillomavirus vaccine; vaccine effectiveness; public health; Cervarix.

Human papillomavirus (HPV) is a sexually transmitted virus that is considered a necessary factor in the development of cervical cancer [1]. Many different HPV types have been identified and classified as high-risk HPV (hrHPV) or low-risk HPV based on their oncogenic potential [2]. HrHPV types 16 and 18 are associated with approximately 71% of all cervical cancer cases. Other hrHPV types frequently identified in cervical cancers (together in approximately 21% of the cancers) are 31, 33, 35, 45, 52, and 58 [3]. Prevention of infection with HPV-16/18 and other hrHPV by means of prophylactic vaccination provides a tremendous opportunity to prevent cancer [4].

To date, 3 vaccines have been licensed for the prevention of HPV-related cancer, providing direct protection against 2, 4, or 9 HPV types. The National Immunization Program of the Netherlands uses the bivalent vaccine Cervarix®, which was licensed in 2007 and targets HPV types 16 and 18 [5]. The Dutch HPV vaccination program started in 2009 with a catch-up campaign for girls born in 1993–1996 (12 to 16 years old). From 2010 onwards, girls are offered vaccination in the year they turn 13, starting with birth cohort 1997 [6].

The bivalent vaccine trials invariably showed high efficacy against persistent HPV-16/18 infection and associated precancer lesions of over 90% [7]. Moreover, some level of cross-protection against nonvaccine hrHPV types was shown in the vaccine trials, but results are less conclusive and dependent on the population and outcome studied [7–10].

Observational studies after the implementation of large-scale immunization programs are important to assess the vaccine effectiveness (VE) against both the vaccine and nonvaccine types in the population at large. Direct effectiveness measures of the bivalent vaccine from observational studies are becoming

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available in the Netherlands [11, 12], as well as other countries [13–16]. These studies showed high VE from a 3-dose schedule against the vaccine types, ranging between 73% and 100% [12–15]. There are also indications for cross-protection of the bivalent vaccine from observational studies; in a recently published paper, high VE against HPV-31, HPV-33, and HPV-45 was observed among women attending their first cervical screening in Scotland [15]. However, type-specific estimates of VE against hrHPV types other than HPV-16/18/31/33/45 are not yet available in a population-based setting.

Knowledge about the cross-protective VE is important to understand the overall VE and potential clinical impact of the bivalent HPV vaccination program. It is also important for vaccine comparisons in health economic assessments [17, 18], especially in view of the more recently licensed nonavalent vaccine that targets 5 additional hrHPV types associated with about 19% of all cervical cancer cases (HPV-31, 33, 45, 52, 58) [19]. Here, we provide direct VE estimates from the bivalent vaccine against hrHPV DNA positivity using cross-sectional data from a biennial survey in Dutch sexually transmitted infection (STI) clinics (PASSYON study). We present the VE against type-specific HPV DNA positivity as well as pooled estimates of VE.

METHODS

Study Design and Population

The PASSYON (PApillomavirus Surveillance among STI clinic YOungsters in the Netherlands) study is a biennial cross-sectional survey among 16 to 24 years old STI clinic visitors that started in 2009, when HPV vaccination was implemented in the Netherlands (Figure 1). The study design is described in detail elsewhere [20]. Briefly, additional to the routine STI consultation, participants were asked to provide a self-collected genital swab for HPV testing and to fill in a questionnaire including self-reported vaccination status. From participants who provided blood for routine syphilis and HIV testing at the STI clinic, serum was collected for HPV serology. Initially, all people attending the STI clinic provided blood, but due to policy changes from 2013 onwards, only specific groups at high risk for syphilis or HIV provided blood. The Medical Ethical Committee of the University of Utrecht, the Netherlands approved this study (protocol number 08/397). Data was obtained anonymously and all participants gave informed consent.

To calculate the VE, we included from the PASSYON study years 2011–2015 all women who had been eligible for vaccination in the Netherlands (ie, women born in 1993 or later [6]), who reported their vaccination status and who provided a vaginal swab.

Laboratory Methods

Swabs were stored at −20°C until analyses. DNA was extracted using the MagnaPure platform (Total Nucleic Acid Isolation Kit, Roche, the Netherlands) and eluted in 100-microliter elution buffer. HPV-DNA was amplified using the SPF_{10} primer set. Subsequently, HPV-specific amplicons were detected using the DNA enzyme-linked immunoassay (HPV-DEIA, DDL Diagnostics Laboratory, the Netherlands). Amplicons of positive samples were genotyped with the Line probe assay ($HPV\text{-}LiPA_{25}$, DDL Diagnostics Laboratory, the Netherlands), which is able to detect the 12 hrHPV types 16/18/31/33/35/39/45/51/52/56/58/59 [20].

Serum samples were stored at −80°C until analyses [21]. HPV antibodies against L1 virus-like particles for types 16 and 18 were assessed using a multiplex immunoassay. Cut-off levels for seropositivity were 9 Luminex Units (LU)/mL for HPV-16 and 13 LU/mL for HPV-18 [22].

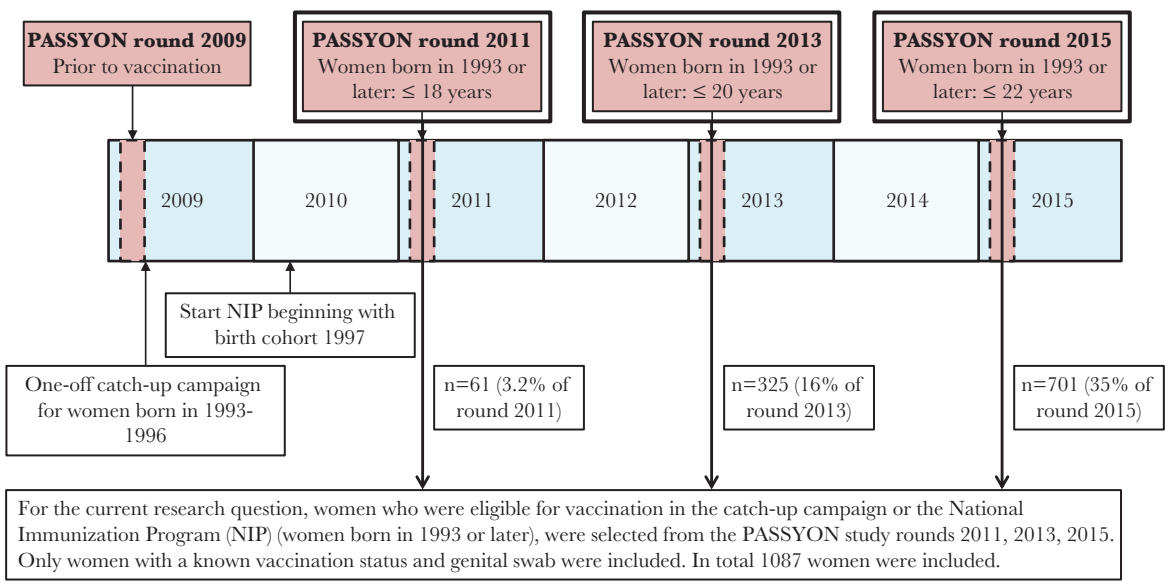

Figure 1. Human papillomavirus (HPV) vaccination in the Netherlands, the PASSYON study design, and the study population selection.

Validation of Self-reported Vaccination Status

We used serology to validate the self-reported vaccination status among those who provided blood. We compared the HPV-16 and HPV-18 seropositivity rates and antibody concentrations between self-reported vaccinated and unvaccinated women. To check the discriminative ability of antibody concentrations with respect to self-reported vaccination status, we calculated the area under the curve (AUC) of a receiver operating characteristic (ROC).

Statistical Analyses

We checked for differences in potential confounders between vaccinated and unvaccinated women using X^2 tests. We included the demographic variables age, ethnicity, and education level. Ethnicity was based on (parental) country of birth. A woman was defined as native Dutch if both parents were born in the Netherlands [23]. Education level was self-reported and categorized as high (school of higher general secondary education, pre-university education, university of applied sciences and university) and low/middle (all other levels of education). We also included the number of sex partners in the past 6 months, number of lifetime sex partners, age at sexual debut (defined as vaginal or anal intercourse), history of STIs, condom use with casual partners in the past 6 months, hormonal contraceptives use, and current genital chlamydia or gonorrhea infection. Chlamydia and gonorrhea infection were diagnosed during the routine STI consultation. The other variables were self-reported and categorized (Table 1).

Vaginal hrHPV DNA positivity was compared between women who reported to be vaccinated at least once and women who reported to be unvaccinated. Outcomes were type-specific hrHPV positivity, the vaccine types HPV-16/18 (pooled), the hrHPV types included in the nonavalent vaccine (HPV-16/18/31/33/45/52/58, pooled), and all hrHPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59, pooled). We used odds ratios (ORs) to estimate the VE, which is suggested to be a suitable measure for the relative reduction in HPV positivity (the combination of incidence and duration of an HPV infection) from cross-sectional data [24]. Because we were interested in the VE on an individual level to give the best approximation of the trial efficacy estimates, we calculated the ORs using a logistic mixed model, incorporating all hrHPV types and a random intercept to account for residual dependence between type-specific infections within individuals. This is an efficient method compared to standard logistic regression, because the covariates' coefficients are estimated from all HPV types simultaneously and the measurement of VE against multiple HPV types (pooled outcomes) is specified as a weighted average [25]. All analyses were adjusted for the variables that were associated with vaccination status ($P < .1$). VE was calculated as 1 minus the adjusted OR times 100% [26].

Because vaccine efficacy is reduced when recipients are HPV positive at vaccination [5, 27], we calculated the VE against the pooled outcomes separately among women who were (possibly) sexually active when vaccination was offered and among women who were not yet sexually active when vaccination was offered. For the catch-up birth cohorts (1993–1996), vaccination of the first dose was offered on 1 March 2009 and for the birth cohorts from 1997 onwards, vaccination of the first dose was offered on 1 March in the year they turned 13 [28]. We compared the self-reported age of sexual debut with the age when vaccination was offered, and categorized women into either not sexually active if the age when vaccination was offered preceded sexual debut, or (possibly) sexually active otherwise (including women who reported the same age of sexual debut as the age when vaccination was offered). Moreover, as cross-protection has been suggested to wane over time [29], we calculated the VE against the pooled outcomes separately among women who were offered vaccination <5 years ago and among women who were offered vaccination 5/6 years ago. This categorization was chosen to have more or less equal numbers in each subgroup. The stratified analyses were adjusted for the variables that were associated with vaccination status ($P < .1$) as well as the age at which the women were offered vaccination.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC), using proc glimmix with adaptive Gauss-Hermite quadrature approximation of the maximum likelihood. We used a significance level of $P < .05$. The records with missing data were excluded from the analyses, as these represented less than 5% of the study population.

Sensitivity Analyses

In sensitivity analyses, we calculated the type-specific and pooled estimates of VE for women who reported to be vaccinated with 3 doses. Moreover, we repeated the stratified analyses, assuming catch-up cohorts were offered vaccination 3 months later, on 31 May 2009 because there was variation in the dates that vaccination was offered during the catch-up campaign [28].

RESULTS

Study Population

In the PASSYON study years 2011–2015, 1198 women had been eligible for HPV vaccination, of which 1087 women reported their vaccination status and provided a vaginal swab (Figure 1). Of these 1087 women, 649 (60%) reported to be vaccinated at least once and 438 (40%) reported to be unvaccinated. Of the women who reported to be vaccinated, 70% (n = 456) reported to be vaccinated with 3 doses, 11% (n = 72) reported less than 3 doses, and 19% (n = 121) reported to not know the number of doses. Of the women who reported to be vaccinated, 94% belonged to the catch-up cohorts (birth cohort 1993–1996).

The characteristics of the study population, stratified by vaccination status, are presented in Table 1. Vaccinated women were more often native Dutch and highly educated. They had

Table 1. Characteristics of the Study Population and a Comparison Between Vaccinated and Unvaccinated Women

	Total	Unvaccinated	Vaccinated (≥1 dose)	
	n (%)	n (%)	n (%)	*P* value[a]
Total	1087	438	649	
Age				.50
16–18 years	325 (29.9)	136 (31.1)	189 (29.1)	
19–22 years	762 (70.1)	302 (68.9)	460 (70.9)	
Ethnicity				<.01
Native Dutch	854 (78.9)	311 (71.3)	543 (83.9)	
Not native Dutch	229 (21.1)	125 (28.7)	104 (16.1)	
Education level[b]				<.01
Low/middle	344 (31.7)	171 (39.0)	173 (26.7)	
High	742 (68.3)	267 (61.0)	475 (73.3)	
Recent sex partners[c]				.02
0–1 partner	310 (28.5)	145 (33.1)	165 (25.4)	
2–3 partners	538 (49.5)	206 (47.0)	332 (51.2)	
≥4 partners	239 (22.0)	87 (19.9)	152 (23.4)	
Lifetime sex partners				.24
0–3 partners	288 (26.9)	127 (29.5)	161 (25.1)	
4–6 partners	346 (32.3)	137 (31.9)	209 (32.6)	
≥7 partners	438 (40.9)	166 (38.6)	272 (42.4)	
Age sexual debut[d]				.06
≤14 years	192 (17.8)	91 (21.0)	101 (15.7)	
15–16 years	558 (51.8)	221 (51.0)	337 (52.3)	
≥17 years	327 (30.4)	121 (27.9)	206 (32.0)	
History of sexually transmitted infections				.03
No	575 (53.1)	213 (48.9)	362 (56.0)	
Yes	241 (22.3)	113 (25.9)	128 (19.8)	
Never tested	267 (24.7)	110 (25.2)	157 (24.3)	
Current genital chlamydia/gonorrhea				.90
No	889 (82.1)	357 (82.3)	532 (82.0)	
Yes	194 (17.9)	77 (17.7)	117 (18.0)	
Condom use with casual partners[c]				.32
(Usually) not	510 (47.0)	199 (45.5)	311 (48.1)	
(Usually) yes	336 (31.0)	132 (30.2)	204 (31.5)	
No casual partners	238 (22.0)	106 (24.3)	132 (20.4)	
Ever used hormonal contraceptives				<.01
No	43 (4.0)	26 (6.0)	17 (2.6)	
Yes	1029 (96.0)	404 (94.0)	625 (97.4)	

[a]Comparing women vaccinated at least once with unvaccinated women.

[b]High educational level included school of higher general secondary education, pre-university education, university of applied sciences and university, low/middle educational level included all other levels of education.

[c]In the past 6 months.

[d]Vaginal or anal intercourse.

Numbers do not always add up to 100% because of missing values.

more partners in the past 6 months, were older at sexual debut, reported less often a history of STIs, and used hormonal contraceptives more often.

Validation of Self-reported Vaccination Status

In total, 43% of the study population had serum available for antibody testing. Of the self-reported vaccinated women, 96% were seropositive for both HPV-16 and HPV-18. Only 11 self-reported vaccinated women (4.2%) were seronegative for HPV-16 or HPV-18 or both (Supplementary Figure 1). Of these 11 women, 8 reported 3 doses, 2 less than 3 doses, and 1 reported not to know the number of doses. The HPV-16 and HPV-18 antibody concentrations agreed well with the self-reported vaccination status (AUC 92.3%).

HPV Prevalence

Overall, 53% tested positive for at least 1 hrHPV type. Of the vaccinated women, 49% were positive for an hrHPV type compared to 59% of the unvaccinated women. HPV-51 was the most prevalent type followed by HPV-52. For most hrHPV types, the

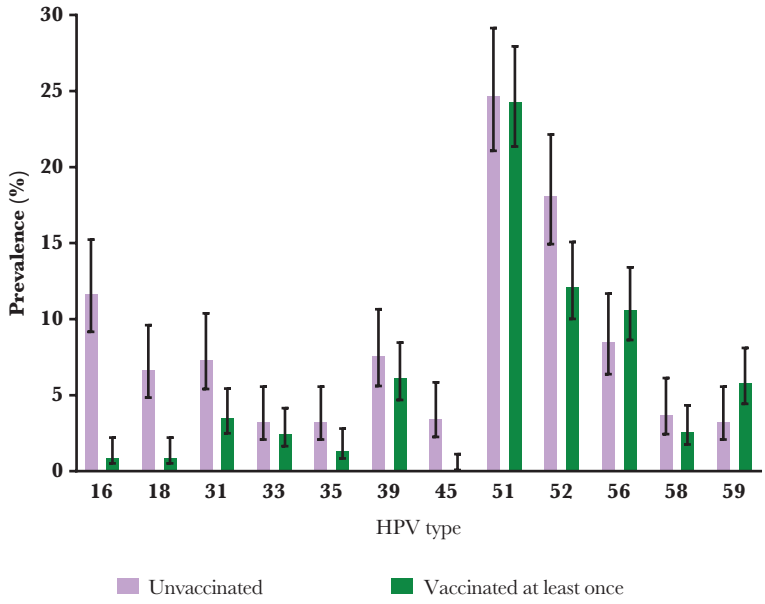

Figure 2. High-risk human papillomavirus (HPV) prevalence by vaccination status.

prevalence was lower for vaccinated compared to unvaccinated women (Figure 2).

Vaccine Effectiveness Estimates

Figure 3 presents the adjusted VE against type-specific hrHPV DNA positivity and against the pooled estimates. The pooled VE against the 2 vaccine types was 89.9%; 92.3% against HPV-16 and 85.5% against HPV-18. Moreover, we calculated significant VE against the nonvaccine types HPV-45, HPV-35, HPV-31, and HPV-52. Although borderline nonsignificant, the VE against HPV-59 was negative (−89%). The pooled VE against the hrHPV types included in the nonavalent vaccine was 60.5% and against all 12 hrHPV types 32.9%.

Results from the stratified analyses are presented in Table 2. Among women who were not sexually active when vaccination was offered, the adjusted pooled VE against the vaccine types (92.2%) was higher than among women who were (possibly) sexually active when vaccination was offered (81.1%). Among women who were offered vaccination 5/6 years ago, we observed similar or higher VE against HPV-16/18 (92.4%), the hrHPV types included in the nonavalent vaccine (65.5%) and all hrHPV types (34.6%) compared to women who were offered vaccination <5 years ago (83.2%, 50.7%, and 33.0%, respectively).

Sensitivity Analyses

The VE estimates according to vaccination with 3 doses are presented in Supplementary Figure 2. Overall, results were comparable to the main analysis. The pooled VE against the vaccine types was somewhat higher; 94.7%. The negative VE against HPV-59 became borderline statistically significant (−107.2%, 95% confidence interval [CI] −307.1 to −5.4). Assuming vaccination for the catch-up cohorts was offered 3 months later did not lead to different results in the stratified analyses (Supplementary Table 1).

DISCUSSION

We demonstrated high VE from the bivalent vaccine against the vaccine types HPV-16/18 and significant cross-protection against the hrHPV types 45, 35, 31, and 52. Together, these cross-protective types are associated with approximately an additional 15% of all cervical cancers [3]. To our knowledge, this is the first observational study reporting VE against hrHPV positivity on a type-specific level for the bivalent vaccine. The cross-protective VE from the bivalent vaccine suggests that the impact of HPV vaccination will be greater than anticipated upon introduction [30].

The high HPV prevalence among STI clinic visitors and sensitive diagnostics to measure infection status, enabled us to measure the type-specific VE against HPV positivity from cross-sectional data. The usefulness of using data from high-risk populations to infer VE in an early stage after the introduction of mass vaccination has been shown by Australian studies; 2 years after HPV vaccination was implemented in Australia, a decline was observed in genital warts among young women and heterosexual men visiting sexual health services [31]. This declining trend was later confirmed in other settings more representative for the general population [32, 33].

We do acknowledge some limitations. First, we used self-reported vaccination status, which is prone to recall bias. The vaccination coverage in our study population was comparable

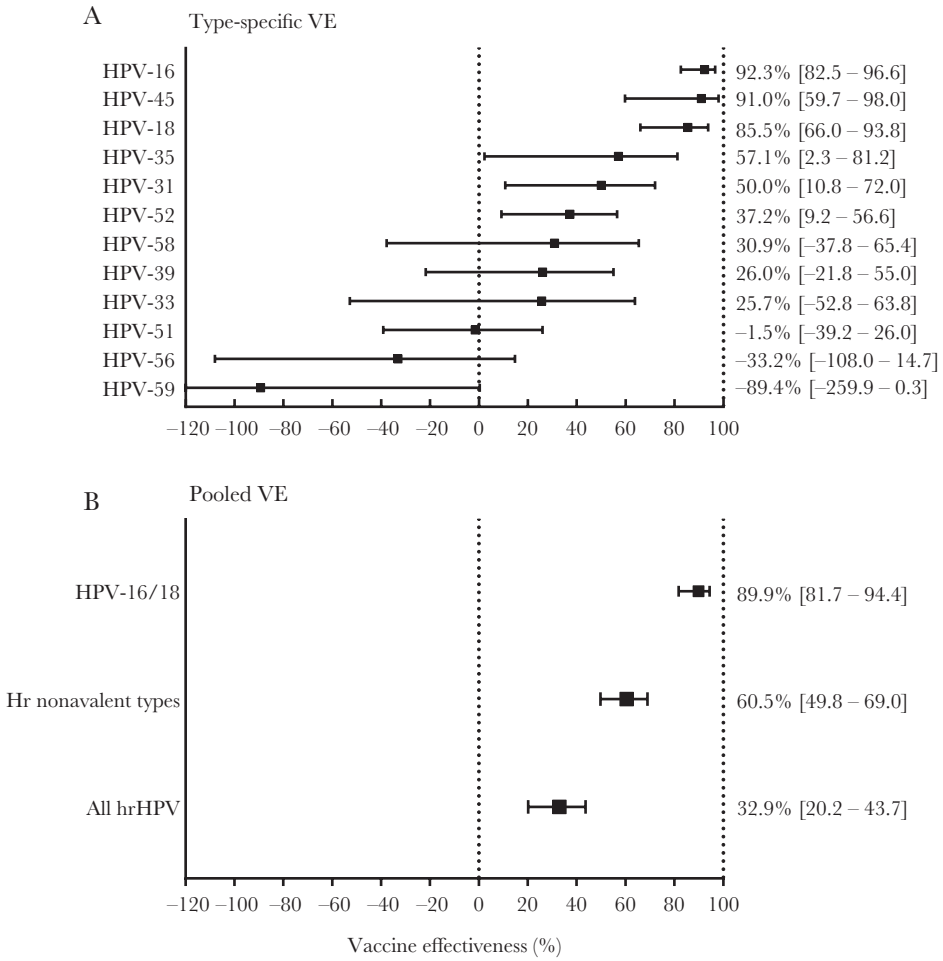

Figure 3. Vaccine effectiveness (VE) for at least one dose against, (*A*) type-specific high-risk (hr) human papillomavirus (HPV) positivity and (*B*) pooled estimates. The hr nonavalent HPV types included: HPV-16/18/31/33/45/52/58. All hrHPV types included: HPV-16/18/31/33/35/39/45/51/52/56/58/59. VE was corrected for: ethnicity, education level, recent sex partners, age at sexual debut, history of sexually transmitted infections, and hormonal contraceptives use.

to the vaccination coverage in the total Dutch population: 52% of the catch-up cohorts received 3 doses and this increased to 59% for birth cohort 1999; an additional 3.8% received less than 3 doses [34–36]. We showed reliable reporting of vaccination status in our study, but we could only validate self-reported vaccination status among women with serum available. Due to the recent policy changes for syphilis and HIV testing at the STI clinic towards high-risk individuals, women with serum available could be biased towards having higher antibody concentrations [37], complicating the distinction between vaccinated and unvaccinated women. Nevertheless, antibody concentrations performed well in discriminating self-reported vaccination status. Moreover, misclassification according to self-reported vaccination status would lead to conservative estimates of VE. Second, because our study population consisted mainly of women who were vaccinated during the catch-up campaign, some women were probably HPV infected at vaccination, leading to lower VE compared to an HPV-naive population [5, 27]. Indeed, we showed a higher VE against the vaccine types among women with a reported sexual debut after vaccination was offered, in line with results from the vaccine trials. Last, most women in our study were vaccinated according to the 3-dose schedule as this was the guideline prevailing at the time of vaccination, so our results might not be generalizable to the current 2-dose schedule. In our study, the VE against the vaccine types was higher for 3 doses compared to at least 1 dose, indicating a lower VE among women who did not know the number of doses or who reported less than 3 doses. Because of a limited number of women who reported having received 2 doses and because we did not known the interval between doses, we were unable to evaluate the current 2-dose schedule with 6 months between doses.

Our results agree well with the literature. Overall, the VE that we calculated against HPV-16/18 positivity and against cross-protective types, are in line with data from the bivalent vaccine trials [7]. In the PATRICIA trial, the largest phase III trial, cross-protection has been described against persistent HPV-31, 33, 45, 51, and 52 infections and against incident HPV-35 infection [8, 9]. In contrast to the PATRICIA trial, we

Table 2. Vaccine Effectiveness Against Pooled Estimates, Stratified by Sexual Activity When Vaccination Was Offered and Time Since Vaccination Was Offered

	n (%)	VE (95% CI)[a]		
		HPV-16/18	Hr nonavalent types[b]	All hrHPV[c]
Women not sexually active when vaccination was offered				
Unvaccinated	303 (37.7)			
Vaccinated (≥1 dose)	501 (62.3)	92.2 (83.2–96.4)	60.1 (47.1–70.0)	29.6 (13.4–42.7)
Women (possibly) sexually active when vaccination was offered[d]				
Unvaccinated	119 (47.6)			
Vaccinated (≥1 dose)	131 (52.4)	81.1 (52.1–92.5)	60.2 (36.2–75.2)	39.9 (16.3–56.8)
Women offered vaccination <5 years ago				
Unvaccinated	178 (43.1)			
Vaccinated (≥1 dose)	235 (56.9)	83.2 (57.9–93.3)	50.7 (23.9–68.1)	33.0 (10.4–49.8)
Women offered vaccination 5/6 years ago				
Unvaccinated	244 (38.1)			
Vaccinated (≥1 dose)	397 (61.9)	92.4 (83.6–96.5)	65.5 (53.9–74.1)	34.6 (19.0–47.2)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; hr, high-risk; VE, vaccine effectiveness.

[a]VE was corrected for: ethnicity, education level, recent sex partners, age at sexual debut, history of sexually transmitted infections, hormonal contraceptives use, and age vaccination was offered.

[b]Including HPV types HPV-16/18/31/33/45/52/58.

[c]Including HPV types HPV-16/18/31/33/35/39/45/51/52/56/58/59.

[d]Includes women who reported the same age (in years) of sexual debut as the age they were offered vaccination.

For the catch-up cohorts, vaccination was offered on 1 March 2009. For the cohorts vaccinated in the National Immunization Program, vaccination was offered on 1 March in the year they turned 13 years old.

did not find statistically significant cross-protection against HPV-33 or HPV-51. In the Costa Rica Vaccine Trial, the efficacy against HPV-33 was, like ours, not statistically significant (32%, 95% CI −41 to 68, against 6-month persistent infection) and against HPV-51 negative (−56%, 95% CI −114 to −14, against 6-month persistent infection) [10]. We found no effect on HPV-51. Effect estimates from observational studies against nonvaccine HPV types are still limited. Trend studies found that the HPV-31/33/45 prevalence decreased in postvaccination periods compared to prevaccination periods, suggestive of cross-protection [38–40]. Among women who underwent their first cervical screening in Scotland, vaccine effectiveness was observed against HPV-31, 33, and 45 [15].

In our study, the VE against the pooled outcomes was similar or even higher among women who were offered vaccination 5 or 6 years ago compared to women who were offered vaccination more recently. These analyses were adjusted for sexual behavior and age when vaccination was offered. These findings are in line with those from Scotland, where high VE against the vaccine types HPV-16/18 and against HPV types 31, 33, and 45 was observed up to 7 years after vaccination [15]. Due to low numbers in the stratified analyses, we were unable to calculate the type-specific VE by time since vaccination was offered. As the PASSYON study continues, we will repeat the analyses to investigate the duration of protection further.

We observed a negative VE against HPV-59, which was just statistically significant in sensitivity analysis restricted to women who reported 3 doses versus no vaccination. The SPF_{10}-$LiPA_{25}$ assay that we used in the current study is very sensitive, but the detection limit for HPV-59 is much higher than for the other hrHPV types, which could lead to an underestimation of the HPV-59 prevalence [41, 42]. Moreover, this assay is a broad-spectrum polymerase chain reaction (PCR) in which some competition between types in the same sample can occur [43]. Possibly due to the reduced occurrence of vaccine and cross-protection types, HPV-59 was more often detected in vaccinated compared to unvaccinated women, which would lead to an artificial negative VE. This phenomenon of increased detection is referred to as unmasking [44]. Another possible explanation for a negative VE is type replacement. This means that an HPV type is taking over the vacated ecological niche of the vaccine and cross-protective types [44]. In post hoc analyses of the PATRICIA trial, an alternative HPV DNA testing algorithm was used including a type-specific test that is not affected by competition between types. Using this type-specific test next to the SPF_{10}-$LiPA_{25}$, the number of HPV-59 cases roughly doubled, but the vaccine efficacy against HPV-59 remained (nonsignificantly) negative for 12-month persistent infection (−29.2%) [9]. Because the sensitivity of the SPF_{10}-$LiPA_{25}$ for HPV-59 is limited and because the confidence intervals were large, the negative VE against HPV-59 in our study should be interpreted with caution. Further research is necessary to investigate what is causing this negative VE estimate.

To conclude, we showed high VE of the bivalent vaccine against HPV-16/18 positivity and significant cross-protection against HPV-45, HPV-35, HPV-31, and HPV-52 in a Dutch high-risk population. We observed cross-protection against 3 of the 5 additional hrHPV types included in the nonavalent vaccine. As the cross-protective types HPV-45, HPV-35, HPV-31,

and HPV-52 are associated with an additional 15% of all cervical cancer cases, cross-protection of the bivalent vaccine can have a major impact on cancer prevention.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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