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High Effectiveness of the Bivalent Human Papillomavirus (HPV) Vaccine Against Incident and Persistent HPV Infections up to 6 Years After Vaccination in Young Dutch Women

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(See the Editorial commentary by Pollock, on pages 1515–6.)

Background. Monitoring vaccine effectiveness (VE) in vaccination programs is of importance for assessing the impact of immunization. This study aimed to estimate the VE of the bivalent human papillomavirus (HPV) vaccine against incident and 12-month persistent infections up to 6 years after vaccination.

Methods. In 2009–2010, girls eligible for the vaccination catch-up campaign (ie, those aged 14–16 years) were enrolled into a prospective cohort. Annually, participants completed a questionnaire and submitted a self-collected vaginal swab sample for HPV testing by the SPF_{10}-$LiPA_{25}$ assay. We compared sociodemographic characteristics and infection rates between vaccinated and unvaccinated girls. The VE was adjusted for characteristics related to HPV vaccination status. We used combined end points for VE estimation.

Results. In total, 1635 women, of whom 54% were fully vaccinated, were included for VE estimation. The adjusted VE against HPV16 and 18 persistent infections amounted to 97.7% (95% confidence interval [CI], 83.5%–99.7%). We found a VE against HPV31, 33, and 45 persistent infections of 61.8% (95% CI, 16.7%–82.5%). We found no indications that the protection against vaccine or cross-protective types changes over time.

Conclusion. Our findings of nearly full protection against vaccine-type persistent infections and significant cross-protection to nonvaccine types in a population-based cohort study confirm the effectiveness of the bivalent HPV vaccine as estimated in trials. We found no indications for waning protection up to 6 years after vaccination.

Keywords. Human papillomavirus (HPV); vaccination; human papillomavirus vaccine; HPV vaccine; effectiveness

Human papillomavirus (HPV) infection is the most common sexually transmitted infection [1]. HPV infection is estimated to cause 5% of all cancers worldwide, both in men and women [2]. The most common cancer associated with HPV among women is cervical cancer, which is the fourth most common cause of cancer among women globally [3]. Since 2006, 3 prophylactic HPV vaccines have been registered. Like many other countries, the Netherlands has implemented HPV vaccination in its national immunization program [4]. HPV vaccination started in 2009, with a catch-up campaign (uptake, 52.3% of individuals) for birth cohorts 1993–1996. From 2010 onward, girls are vaccinated in the year they turn 13 years old (birth cohorts 1997 and onward) [5]. To date, all birth cohorts are vaccinated with the bivalent HPV vaccine, which protects against HPV16 and 18, which are associated with approximately 70% of all cervical cancers. However, the proportions of HPV16 and 18–positive cervical cancers vary by geographic region, with somewhat higher relative contributions in Europe (73%) and North America (79%) [6].

Alongside the introduction of HPV vaccine into the Dutch national immunization program, the Health Council of the Netherlands advised close monitoring of the HPV vaccination program [7]. As cervical cancer screening in the Netherlands only starts at the age of 30 years [8], it will take a long time before the effects of HPV vaccination on clinical end points will become apparent through this program. Meanwhile, the use of intermediate end points, such as persistent HPV infections, will give indications on the effects of the HPV vaccination program [9]. This study aimed to estimate the vaccine effectiveness (VE) of the bivalent HPV vaccine against incident and persistent infections up to 6 years after vaccination, by comparing vaccinated and unvaccinated young women in a prospective cohort study drawn from the general Dutch population.

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METHODS

Study Design

The design of this study has been described previously [10, 11]. In short, 29 162 girls (born in 1993 and 1994) who were eligible for the HPV national catch-up vaccination campaign in 2009 and 2010 at 14–16 years of age were invited to participate in the HPV Amongst Vaccinated and Nonvaccinated Adolescents (HAVANA) prospective cohort study. Of these invited girls, 1832 girls (6.3%) consented to participate. The baseline measurement was performed (approximately 1 month) before vaccination was offered. Both vaccinated and unvaccinated girls were included in the study. Vaccination status of participants was acquired through the national vaccination registration system, Praeventis [12]. Yearly, among all participants, a web-based questionnaire is completed and a vaginal swab specimen is self-collected (Viba-Brush; Rovers Medical Devices, Oss, the Netherlands). This study adhered to the tenets of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam (2009/022). This article describes data up to 6 years after vaccination.

Detection of HPV DNA

Brush samples were stored in 1 mL of phosphate-buffered saline for DNA analysis. Until analyses, swabs were stored at −20°C. DNA extraction was performed using MagNA Pure LC (Total Nucleic Acid Isolation Kit; Roche, Mannheim, Germany) and eluted in 100 µL of elution buffer. The sensitive SPF_{10} primer set was used to amplify HPV DNA. A DNA-specific enzyme-linked immunoassay (HPV-DEIA; DDL Diagnostics Laboratory, Rijswijk, the Netherlands) was used to detect the amplified HPV DNA. Amplicons of samples positive by the HPV-DEIA were genotyped with the reverse line blot assay (HPV-LiPA; DDL Diagnostics Laboratory) which is able to detect 25 HPV genotypes. This assay is able to distinguish the following high-risk types: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Additionally, the assay can detect the following low-risk types: HPV6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 70, and 74. Also HPV68, 73, and 97 can be detected, but these types cannot be distinguished and are therefore all classified as HPV68. HPV68 is considered a putative high-risk type [10].

Statistical Analyses

To be included for these analyses, participants needed to be unvaccinated or fully vaccinated in accordance with the licensed schedule at that time (3 total doses, with 1 each administered at 0, 1, and 6 months) and had a baseline sample available. For participants with missing follow-up data in the surveys, available data from other rounds was used for the analyses. Participants were not censored if they had missed a round of participation (ie, if they did not self-collect a swab specimen in that round but continued participation in a later round) but were censored after their final round of participation.

Differences in sociodemographic and sexual risk factors over time between vaccinated and unvaccinated women were explored using generalized estimating equation (GEE) models with an exchangeable correlation structure. Dichotomous outcomes were analyzed by a binomial model with logit link, resulting in odds ratios (ORs) as the measure of association. For continuous outcomes, we assumed a normal distribution and estimated a mean difference between vaccinated and unvaccinated participants. For outcomes of count data, we used a Poisson distribution, which estimated the rate difference between vaccinated and unvaccinated participants. Potential risk factors were used as dependent variables, and vaccination status was used as an independent variable. First, we checked whether development over time was different between vaccinated and unvaccinated participants by checking the interaction between time and vaccination status. To do this, we added time (as continuous factor) and the interaction between vaccination status and time as independent variables to the model. If a significant interaction between time and vaccination was observed, we reported 3 estimates: one for the vaccination status at baseline, one for time (round of study), and one for the interaction between time and vaccination status. If no significant interaction was observed, the overall estimate (across all time points) for vaccination status was reported.

For all rounds, type-specific HPV prevalence was determined among all participants who had provided a swab for that specific round, independent of their baseline status.

Incidence was defined as being positive for a specific HPV type at that round, preceded by a negative sample in the previous round. Persistence was defined as being HPV positive for a specific HPV type in 2 consecutive rounds, preceded by a negative sample. We calculated the type-specific incidence and persistence rates by GEE, with a Poisson distribution, during follow-up in both vaccinated and unvaccinated participants for high-risk and low-risk types.

We calculated the type-specific VE for all HPV types available in the HPV-LiPA. Owing to limited power to estimate type-specific VE, VE against combined end points was also calculated. Combined end points were vaccine types, cross-protective types, high-risk HPV types, high-risk types included in the nonavalent vaccine, all types included in the nonavalent vaccine, alpha 9 types, alpha 7 types, low-risk types available in the quadrivalent or nonavalent HPV vaccine, low-risk types, and any HPV. To estimate the VE against cross-protective types, we combined HPV31, 33, and 45, for which consistent cross-protective efficacy against 6-month persistent infection and cervical intraepithelial neoplasia grade 2+ was observed in the PATRICIA trial [13, 14]. VE was estimated using the Prentice Williams Peterson total time approach. This is an extension of Cox regression that is able to accommodate recurrent events by taking into account an event-specific hazard for subsequent events [15]. Event-specific hazards were adjusted for time-dependent covariates by using the observed values at each subsequent event. VE was calculated as

1 minus the hazard ratio times 100%. The model for the adjusted VE included characteristics that were significantly ($P < .05$) related to HPV vaccination status in the GEE analysis. To examine the influence of time since vaccination on the VE estimate, we stratified the VE estimates by years since vaccination. Also, the proportionality of hazards over time between vaccinated and unvaccinated participants was explored by adding an interaction term between time and vaccination status to the model.

All analyses were performed using SAS 9.4 (SAS Institute).

Sensitivity Analyses

In sensitivity analyses, we calculated incidence and persistence rates when, instead of 1 round, 2 rounds between infections should have negative test results. Because of the risk for cervical lesions of long-term high-risk HPV infections, in consultation with the medical ethics committee, girls for whom a clinically validated test yielded positive results for the same high-risk HPV type in 3 consecutive rounds should be referred to a gynecologist for further examination. Therefore, girls with positive results of the SPF_{10} assay in 3 consecutive rounds were retested with the clinically validated GP5+/6+ algorithm [16]. If this also yielded 3 positive results of tests for the same high-risk HPV types, girls were referred to a gynecologist. In sensitivity analyses, we censored participants for all HPV types from the moment they were referred to the gynecologist.

RESULTS

Participant Characteristics

For our analyses, at baseline we included 1635 women, of whom 54% were fully vaccinated with a 3-dose schedule. The loss to follow-up over time was approximately 39%. The characteristics of participants over time are presented in Tables 1 and 2. To describe the characteristics over time, we first checked whether there was a difference in development over time between vaccinated and unvaccinated participants by exploring possible interaction between time and vaccination status. If no significant interaction was observed, we reported an overall (for all rounds) estimate. Vaccinated participants were slightly younger than unvaccinated participants (mean difference, −0.14 years; 95% CI, −.21 to −.07). At baseline, vaccinated participants were less likely to live in areas with a lower urbanization degree (OR, 0.33; 95% CI, .26–.43). This difference diminished over time (OR, 1.05 [95% CI, 1.01–1.11] for the interaction between time and vaccination status), but at round 6 vaccinated participants were still less likely to live in areas with a lower urbanization degree (OR, 0.46; 95% CI, .35–.60). At baseline no difference between vaccinated and unvaccinated participants (OR, 0.93; 95% CI, .74–1.15) was observed with regard to contraceptive use (any type). However, over time vaccinated participants became more likely to use contraceptives. At round 6, vaccinated participants had an OR of 3.14 (95% CI, 1.77–5.59) of ever using contraceptives, compared with unvaccinated participants. At baseline, no significant differences were observed between vaccinated and unvaccinated participants with regard to ever having smoked (OR, 0.83; 95% CI, .67–1.01) or ever having sex (OR, 0.86; 95% CI, .70–1.05). Over time, vaccinated participants become more likely to ever have smoked or had sex, as evidenced by significant interactions between time and vaccination status. At round 6, differences between vaccinated and unvaccinated participants with regard to ever having smoked (OR, 1.08; 95% CI, .84–1.38) or ever having sex (OR, 1.42; 95% CI, .94–2.15) were not significant (Table 1). Among sexually experienced participants, additional questions regarding sexual behavior were posed. We did not observe a difference between vaccinated and unvaccinated sexually experienced participants in any of these questions (Table 2).

Prevalence, Incidence, and Persistence of HPV DNA

The proportion of participants positive for any HPV type did not differ significantly between vaccinated and unvaccinated participants but increased significantly over time, from 4.9% (95% CI, 3.3%–6.4%) at baseline to 33.9% (95% CI, 29.7%–38.1%) at the last visit for unvaccinated participants and from 3.3% (95% CI, 2.1%–4.5%) to 36.6% (95% CI, 32.4%–40.7%) for vaccinated participants. The most common high-risk HPV types were HPV51, 16, and 52 among unvaccinated participants and HPV51, 52, and 56 among vaccinated participants (Figure 1A). Among both vaccinated and unvaccinated participants, HPV53 and 66 were the most prevalent low-risk types (Figure 1B). The incidence rate for HPV16 among unvaccinated participants was 22.7 cases per 1000 person-years (95% CI, 18.0–28.6), compared with 3.7 cases per 1000 person-years (95% CI, 2.2–6.4) for the vaccinated group. For HPV18, the incidence rate was 11.7 (95% CI, 8.5–16.2) and 4.0 (95% CI, 2.4–6.8) cases per 1000 person-years, respectively. For persistent infections among vaccinated individuals, the rate was low for HPV16, with 0.3 cases per 1000 person-years (95% CI, 0.0–2.1), and no HPV18 infections were observed (persistence rate, 0.0; 95% CI, .0–1.1). Among unvaccinated participants, the persistence rates were 9.5 cases per 1000 person-years (95% CI, 6.6–13.7) for HPV16 and 4.0 cases per 1000 person-years (95% CI, 2.2–6.9) for HPV18 (Supplementary Materials A).

VE

VE estimates were adjusted for the following factors associated with vaccination status: age, urbanization degree, any history of smoking, any history of contraception use, and any history of sex. We calculated the unadjusted and adjusted VE against type-specific incident and persistent infections with high-risk HPV types (Figure 2). We observed a significant VE for both adjusted and unadjusted estimates for HPV16, 18, 31, and 45 incident infections. In addition, the adjusted VE against incident infections of HPV35 was also significant. For persistent infections, a significant (un)adjusted VE was observed for HPV16, 18, and 31.

Because of the small numbers of type-specific infections, especially for persistent infections, we calculated the unadjusted and

Table 1. Characteristics of Study Participants Over Time

Characteristic, Group	Round 0	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	OR (95% CI)[a]		
								Vaccination Status	Time	Interaction
Vaccination coverage	875 (54)	748 (54)	667 (53)	643 (53)	597 (52)	560 (52)	513 (51)	…	…	…
Age, y, mean (range)										
Unvaccinated	15 (14–17)	16 (15–18)	17 (16–19)	18 (17–20)	19 (18–21)	20 (19–22)	21 (20–23)	Reference	…	…
Vaccinated	15 (14–16)	16 (15–17)	17 (16–18)	18 (17–19)	19 (18–20)	20 (19–21)	21 (20–22)	−0.14 (−.21 to −.07)	…	…
Dutch ethnicity										
Unvaccinated	665 (88)	573 (90)	532 (91)	528 (92)	493 (91)	466 (92)	452 (92)	Reference	…	…
Vaccinated	753 (86)	655 (88)	585 (88)	569 (88)	531 (89)	496 (89)	464 (90)	0.87 (.66–1.17)	…	…
High education level										
Unvaccinated	417 (56)	394 (62)	372 (64)	365 (64)	367 (68)	370 (72)	368 (75)	Reference	…	…
Vaccinated	490 (57)	471 (63)	433 (65)	434 (67)	414 (69)	406 (73)	387 (75)	1.05 (.87–1.27)	…	…
Low urbanization level										
Unvaccinated	227 (31)	202 (32)	177 (30)	173 (31)	145 (27)	118 (23)	114 (23)	Reference	…	…
Vaccinated	114 (13)	95 (13)	83 (12)	82 (14)	72 (12)	61 (11)	54 (11)	0.33 (.26–.43)	0.91 (.88–.94)	1.05 (1.01–1.11)
Ever smoked										
Unvaccinated	248 (38)	264 (42)	259 (44)	299 (53)	284 (53)	291 (57)	285 (58)	Reference	…	…
Vaccinated	267 (32)	303 (41)	271 (41)	335 (52)	335 (56)	319 (57)	299 (58)	0.83 (.67–1.01)	1.18 (1.15–1.22)	1.05 (1.00–1.09)
Current smoker										
Unvaccinated	92 (14)	193 (31)	183 (32)	205 (37)	204 (39)	200 (40)	174 (36)	Reference	…	…
Vaccinated	109 (13)	230 (31)	235 (36)	254 (40)	231 (40)	220 (40)	185 (36)	0.99 (.83–1.17)	…	…
Ever used contraception										
Unvaccinated	314 (42)	370 (59)	420 (73)	467 (84)	477 (89)	462 (91)	447 (93)	Reference	…	…
Vaccinated	332 (38)	460 (63)	515 (78)	558 (89)	550 (94)	528 (96)	489 (96)	0.93 (.74–1.15)	1.78 (1.66–1.91)	1.23 (1.10–1.37)
Ever had sex										
Unvaccinated	210 (28)	275 (44)	331 (58)	398 (71)	424 (79)	427 (84)	420 (87)	Reference	…	…
Vaccinated	187 (22)	316 (43)	397 (60)	439 (70)	480 (82)	479 (86)	450 (88)	0.86 (.70–1.05)	1.69 (1.60–1.79)	1.09 (1.01–1.18)

Data are no. (%) of participants, unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]If a significant interaction between time and vaccination was observed, we report 3 estimates: one for the vaccination status at baseline, one for time (round of study), and one for the interaction between time and vaccination status. If no significant interaction was observed, we report the overall estimate (across all time points) for vaccination status.

Table 2. Sexual Behavior Characteristics Among Sexually Active Participants Over Time

Characteristic, Group	Round 0	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	OR (95% CI)[a]
Aged ≤14 y at sexual debut								
Unvaccinated	104 (50)	87 (35)	76 (25)	79 (21)	78 (19)	76 (19)	73 (18)	Reference
Vaccinated	93 (50)	79 (29)	67 (19)	69 (16)	71 (15)	65 (14)	70 (16)	0.77 (.58–1.01)
Lifetime no. of sex partners, mean (range)[b]								
Unvaccinated	1.7 (1–20)	2.1 (1–15)	2.4 (1–15)	2.8 (1–18)	3.3 (1–22)	4.2 (1–50)	4.6 (1–50)	Reference
Vaccinated	1.7 (1–16)	2.0 (1–15)	2.5 (1–20)	2.8 (1–20)	3.4 (1–31)	4.2 (1–34)	4.8 (1–34)	0.03 (–.07–.13)
Sexually active in past 12 mo								
Unvaccinated		254 (96)	301 (96)	378 (100)	364 (89)	387 (93)	390 (96)	Reference
Vaccinated		292 (94)	368 (95)	425 (100)	413 (88)	435 (94)	417 (95)	0.93 (.68–1.26)
New no. of sex partners in past 12 mo, mean (range)[b]								
Unvaccinated		1.2 (0–10)	1.0 (0–6)	1.0 (0–7)	1.1 (0–12)	1.2 (0–31)	1.0 (0–17)	Reference
Vaccinated		1.2 (0–7)	1.2 (0–12)	1.0 (0–13)	1.1 (0–11)	1.2 (0–16)	1.0 (0–14)	0.07 (–.06–.20)
Has current sex partner								
Unvaccinated	155 (73)	192 (76)	238 (79)	285 (75)	301 (77)	319 (79)	336 (82)	Reference
Vaccinated	117 (63)	197 (67)	278 (76)	323 (76)	349 (75)	348 (79)	348 (79)	0.95 (.82–1.10)
Age in years of current sex partner, mean (range)								
Unvaccinated	17.2 (13–23)	18.0 (14–26)	19.1 (15–27)	20.7 (16–48)	21.8 (16–44)	22.8 (17–45)	24.0 (18–46)	Reference
Vaccinated	17.2 (15–23)	18.1 (14–24)	19.2 (15–30)	20.4 (16–39)	21.5 (17–45)	22.5 (17–34)	23.5 (19–44)	−0.19 (–.53–.16)
Had STI diagnosed in past 12 mo								
Unvaccinated	2 (1)	5 (2)	5 (2)	6 (2)	7 (3)	22 (5)	14 (3)	Reference
Vaccinated	2 (1)	3 (1)	8 (2)	19 (4)	3 (4)	22 (5)	24 (5)	1.32 (.88–2.00)

Data are no. (%) of participants, unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio; STI, sexually transmitted infection.

[a]There was no significant interaction between time and vaccination, so we report the overall estimate (across all time points) for vaccination status.

[b]Rate difference was calculated.

adjusted VE also against combined end points (Figure 3). The adjusted VE against incident and persistent infections caused by vaccine types HPV16 and 18 was 77.5% (95% CI, 64.9%–85.6%) and 97.7% (95% CI, 83.5%–99.7%), respectively. We observed a cross-protective VE against HPV31, 33, and 45 combined of 55.9% (95% CI, 33.2%–70.9%), when considering incident infections, and 61.8% (95% CI, 16.7%–82.5%), when considering persistent infections. The combined adjusted VE against all HPV types included in the nonavalent vaccine (ie, HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) was 33.0% (95% CI, 19.1%–44.6%) for incident infections and 50.4% (95% CI, 29.7%–65.1%) for persistent infections. We did not find any indication that the VE against vaccine types (ie, HPV16 and 18) and cross-protective types (ie, HPV31, 33, and 45) wanes over time (Supplementary Materials *B*).

Sensitivity Analyses

We found the same HPV types to have significantly lower incidence or persistence rates in vaccinated participants when at least 2 negative test results between consecutive infections were required for incidence and persistence (Supplementary Materials *C*). Censoring participants (n = 13) when they were referred to a gynecologist did not influence our VE estimates (data not shown).

DISCUSSION

We estimated the VE against incident and 12-month persistent HPV infections up to 6 years after vaccination in an ongoing longitudinal observational study among vaccinated and unvaccinated women in the Netherlands. We found a very high VE against incident and persistent infections by vaccine types HPV16 and 18 and good cross-protection against HPV31, 33, and 45 combined. We did not find indications that protection against vaccine or cross-protective types wanes over time. These findings are reassuring with regard to expected benefits of the bivalent HPV vaccination program on a population-level.

The World Health Organization considers persistent HPV infections (defined as those with a duration of ≥6 months) as an intermediate end point in the evaluation of HPV vaccination [9]. We observed a very high VE (97.7%; 95% CI, 83.5%–99.7%) against 12-month persistent infections with HPV16 and 18 among girls. Our findings are in line with the original bivalent vaccine trials examining the efficacy against 6-month persistent infections related to HPV16 and 18, where the efficacy was also >90% [17]. It should be noted that the definitions of incident and persistent infections require HPV-positive samples to be proceeded by an HPV-negative sample. In previous studies, consistent evidence of cross-protective efficacy was shown against HPV31, 33, and 45 [18]. In contrast to these studies, we did not observe a significant protective VE against incident and persistent HPV33 infections. Our findings with regard to the estimated combined VE against HPV31, 33, and 45 are in line with observational data from Scotland among participants in a cervical cancer screening program, for whom the prevalence of

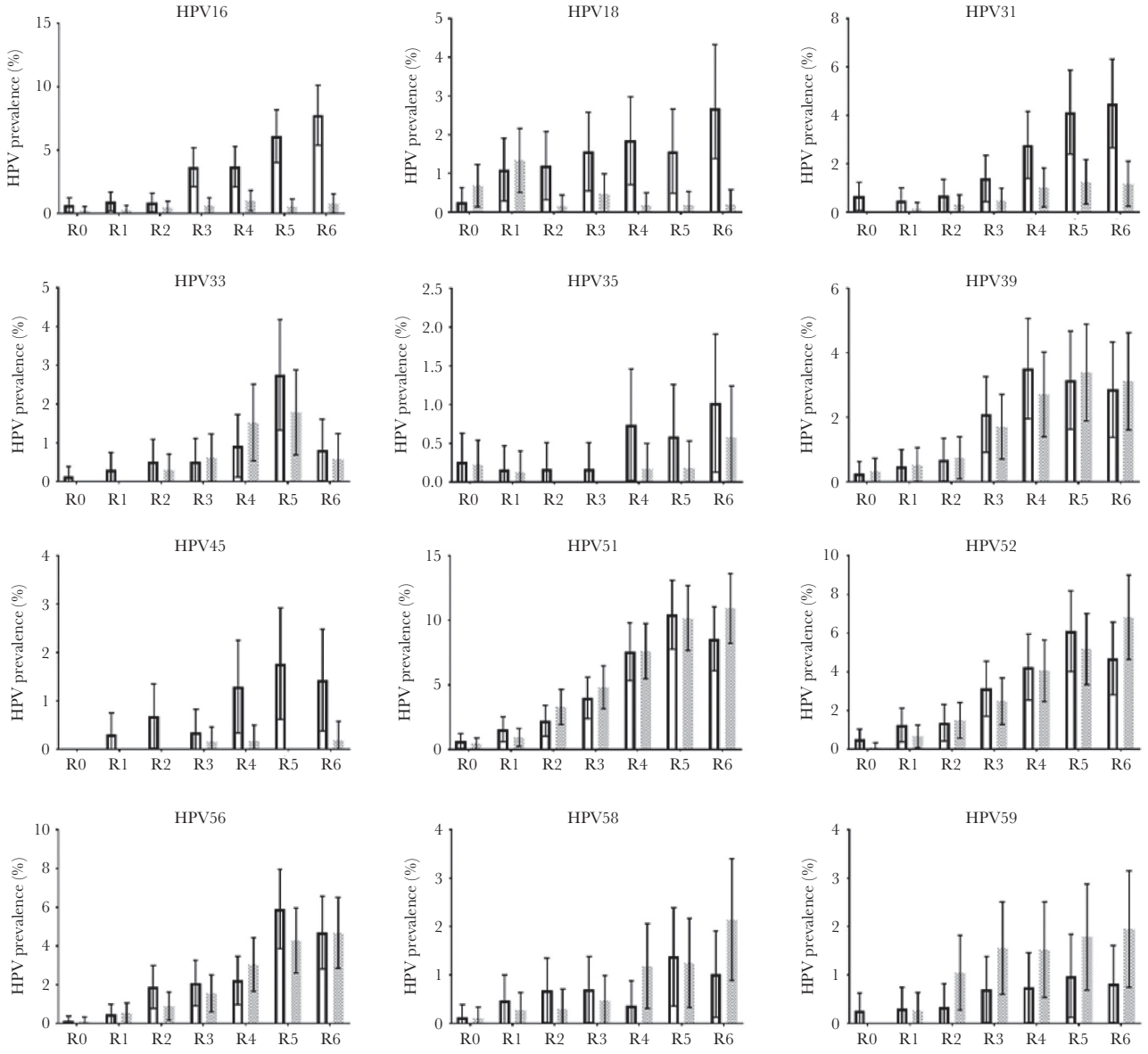

Figure 1. *A,* Type-specific human papillomavirus (HPV) prevalence for high-risk types during follow-up among vaccinated and unvaccinated participants of the HAVANA study. *B,* Type-specific HPV prevalence for low-risk types during follow-up among vaccinated and unvaccinated participants of the HAVANA study. *HPV68: No distinction can be made between HPV68, 73, and 97, so all are classified as HPV68. *y*-axes for different HPV types might differ. Black denotes the prevalence among unvaccinated participants, and gray denotes the prevalence among fully vaccinated individuals. R, round.

HPV31, 33, and 45 among girls vaccinated at the age of 15 and 16 years decreased by 69.2% and 56.8%, respectively, 7 years after vaccination. Compared with this age group, the Scottish study observed a slightly higher (but not significantly different) VE among girls vaccinated at the age of 12–13 years (VE, 85.1%; 95% CI, 77.3%–90.9%) [19]. Data from Scotland have also shown significant reductions in low- and high-grade CIN [20]. Recently Tota et al suggested some protective effect against incident infections with HPV35, 52, and 58 by combining data from the Costa Rica Vaccine Trial and the PATRICIA trial [21]. After adjustment, we also observed cross-protection against HPV35 incident infections (adjusted VE, 70.8%; 95% CI, 8.1%–90.7%), but we did not find indication of a cross-protective effect against HPV52 and 58.

We did not observe a difference in protection over time, neither for vaccine types nor for cross-protective types. Hence, no indications of waning protection were found in our study population up to 6 years after vaccination. This is in line with recently published findings from a Dutch study among visitors to a sexually transmitted infection (STI) clinic [22] and from a Scottish study [19], where no indications for waning protection against prevalent infection due to vaccine types and cross-protective types were observed. These finding are in contrast to those of a meta-analysis of vaccination trials [23]. It could be

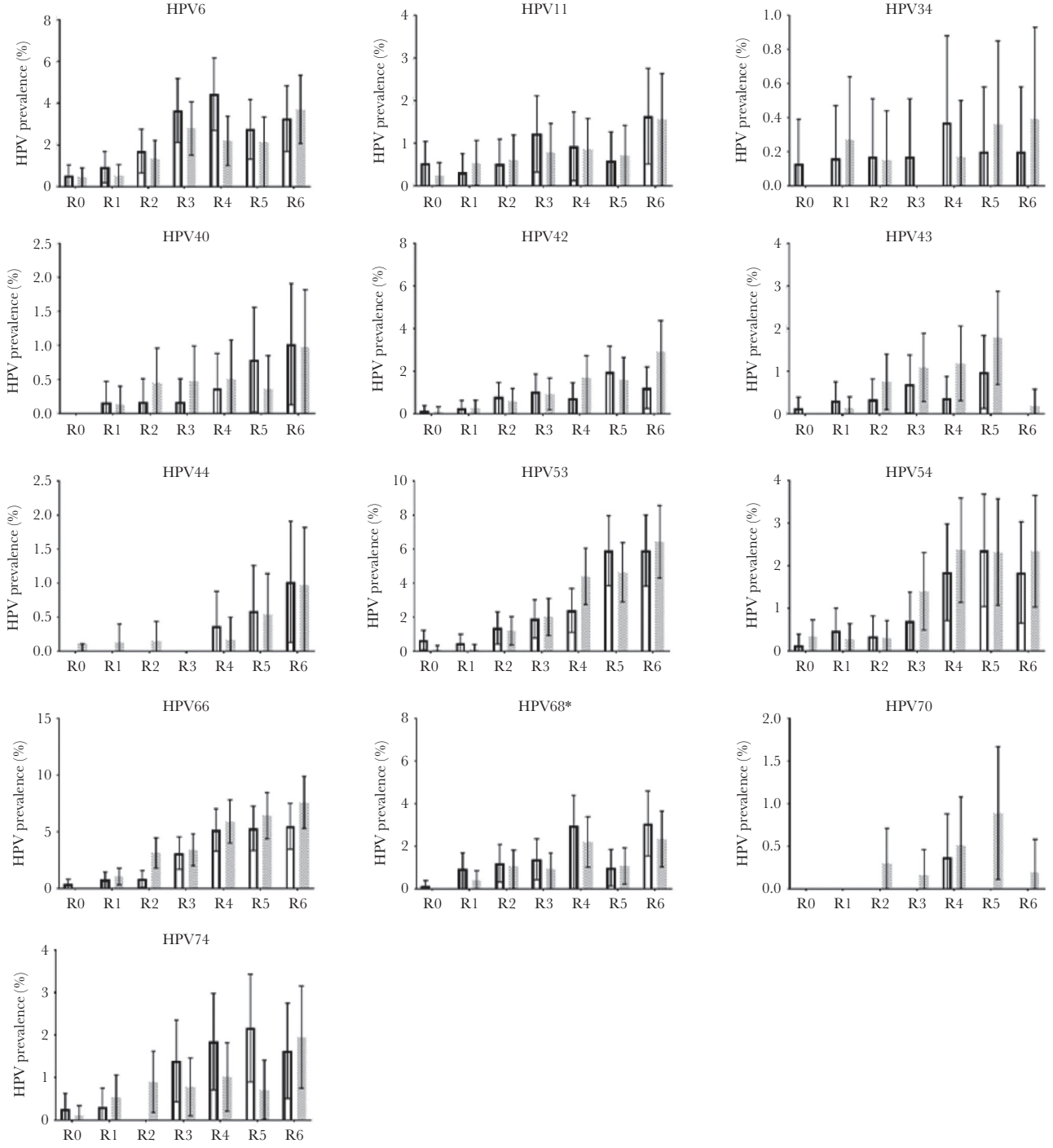

Figure 1. Continued

that women in these trials were more frequently exposed to HPV than our study participants (eg, trial participants were older than our study participants). On the other hand, differences between studies included in the meta-analysis might be explained by systematic differences between study populations or trial protocols. Our longitudinal follow-up study was appropriate for detecting a change in protection over time, but it might be underpowered because of the limited exposure of our cohort at this time. Further follow-up of our cohort is needed to confirm that protection is not waning.

We examined possible differences between vaccinated and unvaccinated participants and explored whether differences in development over time between study groups exist. Differences might be due to preexisting differences among girls who accepted vaccination and those who did not. Alternatively, different trends over time could be due to changes in behavior as an

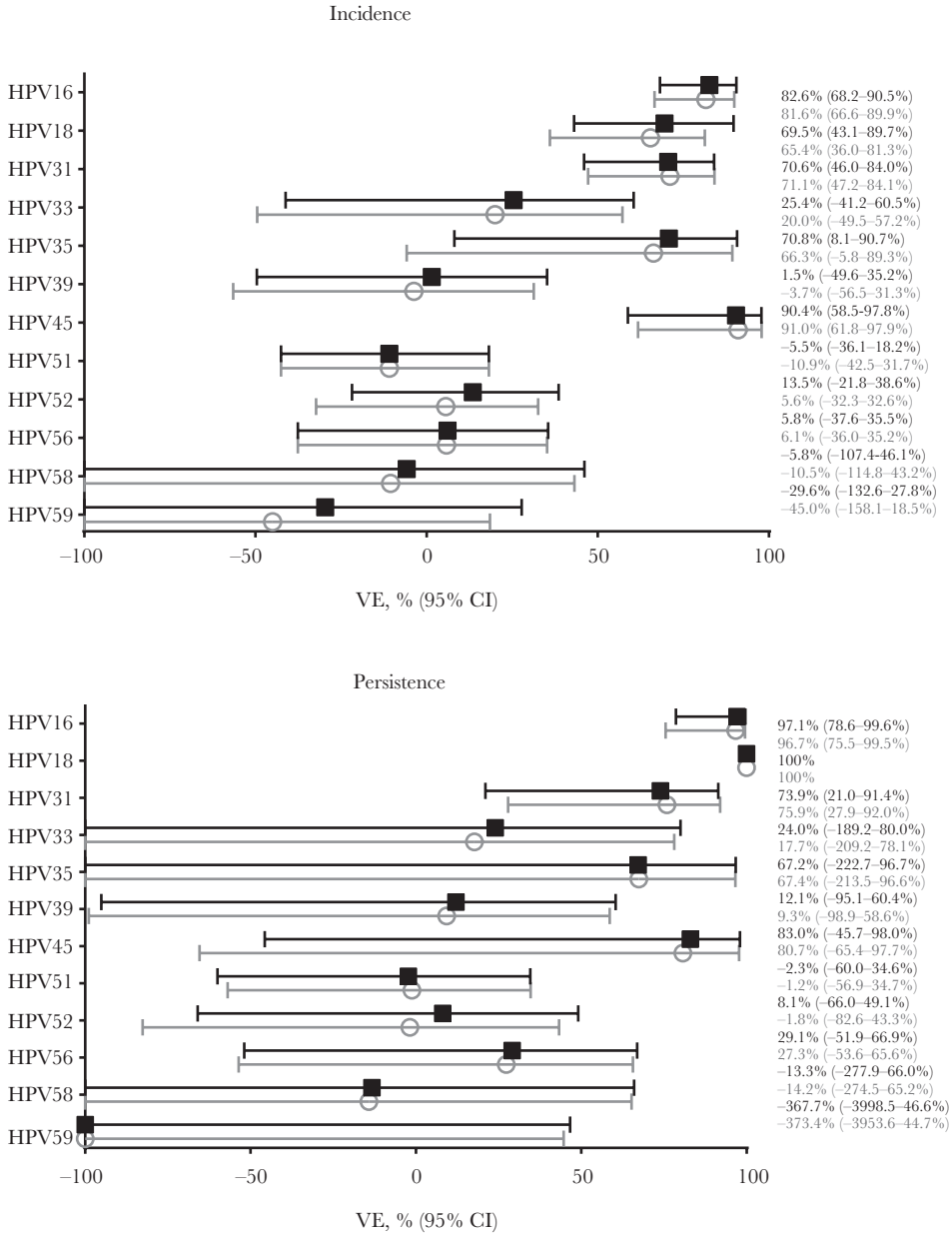

Figure 2. (Un)adjusted type-specific vaccine effectiveness (VE) against incident and persistent infections up to 6 years after vaccination. CI, confidence interval; HPV, human papillomavirus.

indirect effect of vaccination. In our cohort, vaccinated participants were less likely to live in areas with a lower urbanization level and more likely to have ever smoked, used contraception, and had sex. Besides differences in ever having sex, we did not observe any difference in sexual behavior between vaccinated and unvaccinated participants. These findings are in line with previous Dutch studies on uptake of vaccination [24, 25] and sexual behavior after HPV vaccination [24, 26]. Besides comparability with regard to sociodemographic and sexual risk factors, comparability with regard to exposure to HPV can be examined. We did not observe a significant difference between vaccinated and unvaccinated participants in the prevalence of any HPV.

In contrast to post hoc analyses of the PATRICIA trial, where significant protection against 6-month persistent infection due to HPV6 and 11 was observed [27], we did not observe an effect of the bivalent vaccine against incident and persistent HPV6 and 11 infections in our study. These findings are in line with those of a previous Dutch study, where no effect of the bivalent vaccine was found against the HPV6 and 11 prevalence among STI clinic visitors. However, that study did find a nonsignificant partially protective effect against anogenital warts [28]. Data from England have shown a significant decline in genital warts after the introduction of the bivalent vaccine for young girls and heterosexual men [29].

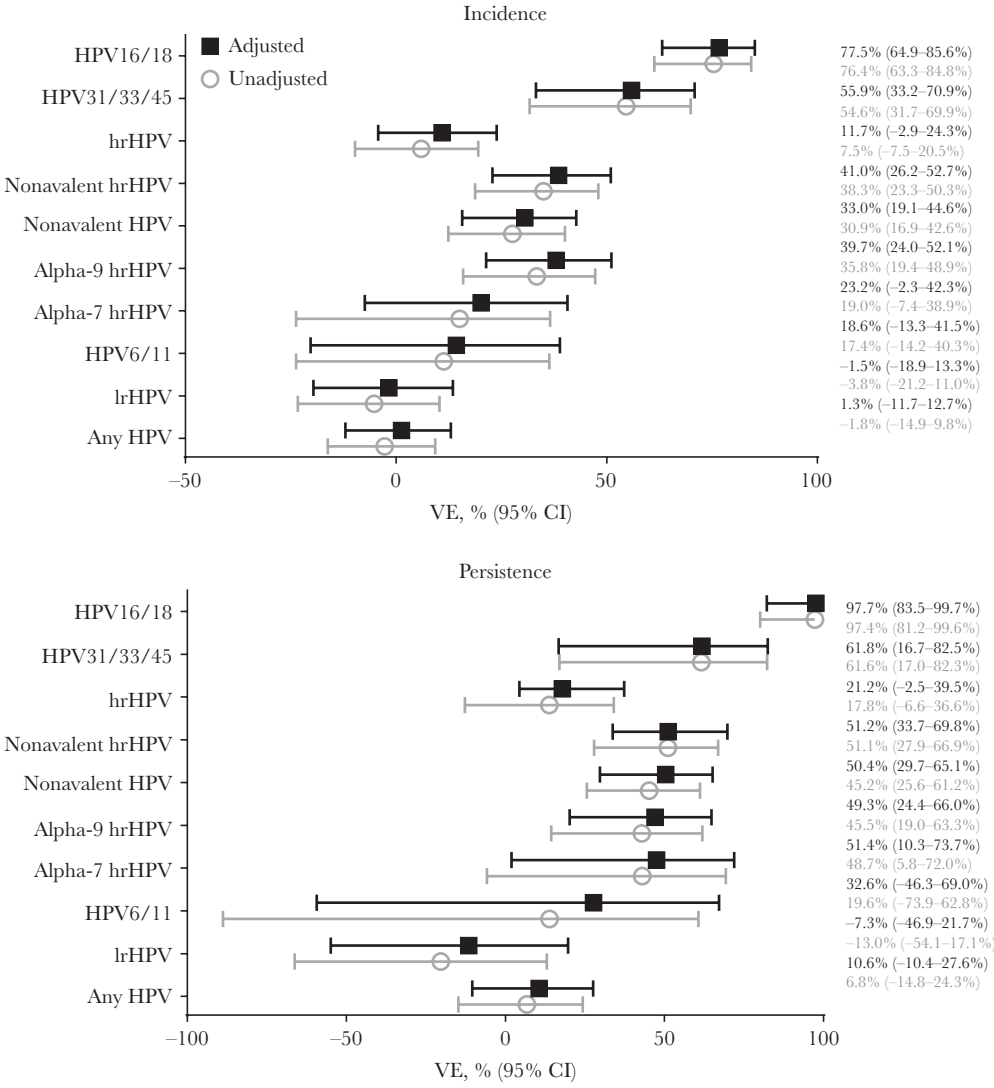

Figure 3. (Un)adjusted vaccine effectiveness (VE) against incident and persistent infections up to 6 years after vaccination. Nonavalent includes all 9 types included in the nonavalent human papillomavirus (HPV) vaccine (HPV6/11/16/18/31/33/45/52/58), while nonavalent high-risk HPV (hrHPV) includes only the 7 hrHPV types (HPV16/18/31/33/45/52/58) included in the nonavalent vaccine. alpha-9 high-risk HPV types include HPV16/31/33/35/52/58, and alpha-7 hrHPV types include HPV18/39/45/59. CI, confidence interval; lrHPV, low-risk HPV.

We acknowledge some limitations of our study. First, given the low participation rate of the study, results found in our study participants might not be representative of the Dutch population. Previously, study participants in the HAVANA cohort study were compared to the general Dutch population with regard to education level, ethnicity, and age of sexual debut. Participants in our study were more educated and less likely to be a second-generation migrant [11]. However, the proportion of women in our study who ever had sex was comparable to that in the general population; therefore, we think this selection bias had limited influence on our estimates [30]. Second, women included in this study were eligible for the HPV vaccination catch-up campaign and therefore slightly older than girls included in the routine program. Given the older age of the former group, it is more likely that they might have been sexually active and, in turn, infected with HPV before vaccination. Last, although we had a long follow-up period (up to 6 years after vaccination), we still had low power in obtaining type-specific VE estimates.

In conclusion, this population-based observational study allows the monitoring of VE against intermediate end points during longitudinal follow-up. We observed high VE against incident and persistent infections due to vaccine types HPV16 and 18 and cross-protection against oncogenic types. We did not find indications that cross-protection against HPV 31, 33, and 45 might wane over time up to 6 years after vaccination.

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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Potential conflicts of interest. C. J. L. M. M. has received speakers' fee from SPMSD/Merck; has served occasionally on the scientific advisory board (expert meeting) of Qiagen and SPMSD/Merck; has been coinvestigator on a Sanofi Pasteur MSD–sponsored trial; is part-time director of and minority stock holder of Self-Screen, a spin off company of VU University Medical Center; has a very small number of Qiagen shares; and, until April 2016, had minority stock of Diassay. All author others report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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