The Journal of Infectious Diseases

BRIEF REPORT

Bivalent Vaccine Effectiveness Against Anal Human Papillomavirus Positivity Among Female Sexually Transmitted Infection Clinic Visitors in the Netherlands

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(See the Editorial Commentary by Clifford and Combes, on pages 1210–2.)

Human papillomavirus (HPV) vaccines are indicated for anal cancer prevention, but evidence for vaccine effectiveness (VE) against anal HPV infections among women is limited. We estimated the VE (≥1 dose) against anal HPV positivity of the bivalent vaccine, whose target types HPV-16/18 are associated with approximately 90% of HPV-related anal cancers. Among 548 female STI clinic visitors 16–24 years old who provided an anal swab sample as part of a repeated cross-sectional survey, VE against HPV-16/18 was 89.9% (95% confidence interval, 63.0%–97.2%). Type-specific VE correlated well with VE against cervicovaginal HPV (Spearman $\rho = 0.76$), suggesting comparable effectiveness of HPV-16/18 vaccination against genital and anal infections.

Keywords. Human papillomavirus (HPV); human papillomavirus vaccine; vaccine effectiveness; public health; anal cancer.

The sexually transmitted human papillomavirus (HPV) plays a causal role in the development of cervical, vaginal, vulvar, penile, oropharyngeal, and anal cancers. Anal cancer is more prevalent among women than among men and is responsible for the second largest HPV-related disease burden among women after cervical cancer [1]. The share of anal cancer in the total HPV-related disease burden is steadily increasing in many countries, owing to rising incidence trends and a current lack of effective screening opportunities [2]. Worldwide, >20 000 women are affected by anal cancer each year, of which approximately 88% are caused by oncogenic HPV infections, mainly HPV-16/18 [1].

HPV vaccines hold promise for anal cancer control. However, though the high vaccine effectiveness (VE) of prophylactic HPV vaccines against cervicovaginal HPV infections has been widely documented in both randomized controlled trials (RCTs) and postmarketing studies, data on VE against anal HPV infections are scarce, especially among women. In 1 RCT of the bivalent vaccine, post hoc analyses demonstrated strong protection against anal positivity with vaccine types HPV-16/18 (vaccine efficacy, 83.6% in the per-protocol population) and significant cross-protection against HPV-31 and HPV-45 [3].

In 2 other RCTs of the quadrivalent HPV vaccine, vaccine efficacy against anal HPV infections was estimated among men. In the per-protocol populations, vaccination afforded strong protection against anal persistent HPV-16/18 infection (vaccine efficacy, >95%) [4, 5]. In addition, efficacy against high-grade anal intraepithelial neoplasia was demonstrated among men who have sex with men (vaccine efficacy, 74.9%) [4]. Based on the latter study, the HPV vaccines received an indication for the prevention of anal cancer. One observational study of the quadrivalent vaccine explored the association between vaccination and anal HPV positivity among high-risk women and found a 64% reduction in the detection of anal HPV-6/11/16/18 infections [6]. So far, postmarketing evidence on protection against anal HPV infection by the bivalent HPV vaccine has not become available.

The Netherlands has consistently used the bivalent vaccine (Cervarix; GSK) in the national immunization program. Large-scale vaccination started in 2009 with a catch-up campaign for girls born in 1993–1996. Routine HPV vaccination was introduced in 2010 for girls in the year they turn 13 years old. We previously reported on type-specific VE of the bivalent HPV vaccine against cervicovaginal HPV positivity [7]. In the current study, we evaluated VE against anal HPV positivity among female visitors to sexually transmitted infection (STI) clinics in the Netherlands.

METHODS

We used the same methods to estimate the VE against anal HPV positivity as previously used to estimate VE against cervicovaginal HPV positivity [7]. In short, we used data from the papillomavirus surveillance among STI clinic youngsters in the Netherlands (PASSYON) study. In this biennial cross-sectional study that started in 2009, 16–24-year-old visitors to STI clinics in the Netherlands were asked to provide a self-collected genital swab sample and to fill-in a questionnaire, including self-reported HPV vaccination status. A random subset of women

Received 4 March 2019; editorial decision 20 March 2019; accepted 17 April 2019; published online April 23, 2019.

[a]Membership of the Medical Microbiological Laboratories and Public Health Services is provided in the Acknowledgments.

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The Journal of Infectious Diseases® 2020;221:1280–5

DOI: 10.1093/infdis/jiz187

were also asked to provide a self-collected anal swab sample on a voluntary basis. Because of financial constraints, not all women were asked for an anal swab sample; in the PASSYON study years 2015 and 2017, we aimed to obtain anal swab samples from a convenience sample of about 30% of the women, irrespective of self-reported vaccination status or sexual risk behavior.

Women who agreed to provide an anal swab sample were instructed to insert a swab about 3 cm into the anus and circle it around for 5–10 seconds. Swab samples were tested using the SPF10 DEIA-LiPA25 assay (DDL Diagnostics Laboratory). This broad-spectrum polymerase chain reaction assay can detect DNA of several HPV types, including the high-risk HPV (hrHPV) types 16/18/31/33/35/39/45/51/52/56/58/59 and the low-risk HPV types HPV-6/11. All participants provided informed consent.

For the current research question, we included women who had been eligible for HPV vaccination in the Netherlands (ie, women born since 1993), reported their vaccination status, and provided an anal swab sample. We included data from the PASSYON study years 2011–2017.

Anal HPV positivity was compared between women who reported being vaccinated (≥1 dose) and those who reported not being vaccinated. To estimate the VE against anal HPV positivity, we used logistic mixed models with a random intercept, incorporating all clinically relevant HPV types (hrHPV and HPV-6/11). Outcomes were type-specific HPV positivity, positivity for the vaccine types (HPV-16/18, pooled), for the HPV types included in the nonavalent vaccine (HPV-6/11/16/18/31/33/45/52/58, pooled), and for all acknowledged hrHPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59, pooled). The pooled estimates were obtained as weighted averages of type-specific estimates. The analyses were adjusted for age and the variables that were found with χ^2 tests to be associated with vaccination status (at a $P < .1$ level). VE was estimated as (1 − adjusted odds ratio) × 100%.

Next, we assessed the Spearman rank correlation between the type-specific anal and cervicovaginal VE estimates. The VE against cervicovaginal HPV positivity was estimated using the same study population and method used for estimating VE against anal HPV positivity.

As sensitivity analyses, we estimated the VE against anal HPV positivity restricted to women who reported any history of anal sex (ie, those considered at increased risk for anal cancer [8]) or restricted to women who were offered vaccination ≥5 years ago, comparable to previous analyses [7].

All analyses were performed using SAS software, version 9.4 (SAS Institute), with a significance level of $P < .05$. Records with missing data were excluded from the analyses, because these represented <5% of the study population.

RESULTS

In the PASSYON study (years 2011–2017), a total of 2413 women were eligible for HPV vaccination in the Dutch national immunization program, of whom 2246 reported their vaccination status. Of these women, 548 (24%) provided an anal swab sample (Supplementary Figure 1). Demographics and sexual risk behavior differed between women who provided an anal swab sample and those who did not, possibly related to the willingness of women to collect the sample. For example, anal swab samples were available for 51% of the women who reported anal sex in the past 6 months, compared with 19% of those who reported no history of anal sex. Whether or not women provided an anal swab sample also differed by vaccination status. For instance, among women who reported no history of anal sex, vaccinated women were more likely than unvaccinated women to provide a sample (21% vs 15%, respectively) (Supplementary Table 1).

Of the 548 women who did provide an anal swab sample and were included in the statistical analyses, 357 (65%) reported being vaccinated with ≥1 dose (43 women reported incomplete dosing). Vaccinated women were more likely to report a high education level and less likely to report any history of anal sex, reported more sex partners in the past 6 months, and were less likely to report STI-related symptoms and more likely to report hormonal contraceptive use (Table 1). The VE measures were adjusted for all these variables.

Only 2 vaccinated women (0.6%) tested positive for anal HPV-16, and only 1 (0.3%) for HPV-18 (Supplementary Table 2). In comparison, 4.2% and 3.1% of unvaccinated women tested positive for anal HPV-16 and HPV-18, respectively, leading to adjusted VEs of 88.2% (95% confidence interval [CI], 41.3%–97.6%) against anal HPV-16 and 91.9% (95% CI, 30.5%–99.1%) against anal HPV-18 (Figure 1). The VE against anal HPV-16/18 combined was 89.9% (95% CI, 63.0%–97.2%). None of the vaccinated women were positive for anal HPV-45, compared with 3.1% of the unvaccinated women (VE, 100%; unadjusted 95% CI, 66.5%–100%). We also observed cross-protection against anal HPV-31 (VE, 73.0%; 95% CI, 25.5%–90.2%). The type-specific VE against anal HPV positivity correlated well with the VE against cervicovaginal HPV positivity (Spearman rank correlation, $\rho = 0.76$; $P < .01$).

Of the total study population, 251 women (46%) reported any history of anal sex. In this subgroup, the anal prevalence of an hrHPV type or HPV-6/11 was higher than among women who reported no history of anal sex (41% vs 34% respectively), and the VE against anal HPV-16/18 was 95.5% (95% CI, 63.3%–99.5%) (Supplementary Figure 2). Most women (n = 491 [90%]) were offered vaccination ≥5 years ago (range, 5–8 years). In this subgroup, the VE against anal HPV-16/18 was comparable to that in the total population, at 90.0% (95% CI, 63.3%–97.3%) (Supplementary Figure 3).

DISCUSSION

We demonstrated high effectiveness of the bivalent HPV vaccine against anal positivity with vaccine types HPV-16/18

Table 1. Characteristics of the Study Population Used to Estimate Vaccine Effectiveness Against Anal Human Papillomavirus Positivity

Characteristic	Participants, No. (%)[a]			*P* Value (χ^2 Test)
	Total (N = 548)	Unvaccinated (n = 191)	Vaccinated (≥1 dose) (n = 357)	
Age				.36
16–18 y	72 (13.1)	29 (15.2)	43 (12.0)	
19–21 y	330 (60.2)	117 (61.3)	213 (59.7)	
22–24 y	146 (26.6)	45 (23.6)	101 (28.3)	
Migration background[b]				.10
Native Dutch	420 (76.8)	139 (72.8)	281 (78.9)	
Not native Dutch	127 (23.2)	52 (27.2)	75 (21.1)	
Education level[c]				<.01
Low/middle	115 (21.0)	55 (28.8)	60 (16.8)	
High	433 (79.0)	136 (71.2)	297 (83.2)	
History of anal sex				.02
No	295 (54.0)	91 (47.9)	204 (57.3)	
Yes, in past 6 mo	142 (26.0)	63 (33.2)	79 (22.2)	
Yes, ever	109 (20.0)	36 (18.9)	73 (20.5)	
No. of sex partners in past 6 mo[d]				.05
0–1	133 (24.3)	55 (28.9)	78 (21.8)	
2–3	263 (48.1)	93 (48.9)	170 (47.6)	
≥4	151 (27.6)	42 (22.1)	109 (30.5)	
No. of lifetime sex partners[d]				.18
0–3	110 (20.4)	46 (24.7)	64 (18.1)	
4–6	142 (26.3)	48 (25.8)	94 (26.6)	
≥7	288 (53.3)	92 (49.5)	196 (55.4)	
Age at first sexual intercourse[d]				.96
≤14 y	75 (13.8)	25 (13.4)	50 (14.1)	
15–16 y	283 (52.2)	99 (52.9)	184 (51.8)	
≥17 y	184 (33.9)	63 (33.7)	121 (34.1)	
Self-reported history of any STI				.60
No	291 (53.1)	97 (50.8)	194 (54.3)	
Yes	155 (28.3)	59 (30.9)	96 (26.9)	
Never tested	102 (18.6)	35 (18.3)	67 (18.8)	
Current anal chlamydia/gonorrhea				.28
No	173 (31.6)	68 (35.6)	105 (29.4)	
Yes	32 (5.8)	12 (6.3)	20 (5.6)	
Not tested	343 (62.6)	111 (58.1)	232 (65.0)	
Notified for STIs				.59
No	468 (85.4)	161 (84.3)	307 (86.0)	
Yes	80 (14.6)	30 (15.7)	50 (14.0)	
STI-related symptoms				.05
No	411 (75.1)	134 (70.2)	277 (77.8)	
Yes	136 (24.9)	57 (29.8)	79 (22.2)	
Condom use past in 6 mo with casual partners				.24
No (usually)	254 (46.7)	83 (43.9)	171 (48.2)	
Yes (usually)	190 (34.9)	64 (33.9)	126 (35.5)	
No casual partners	100 (18.4)	42 (22.2)	58 (16.3)	
History of using hormonal contraceptives				<.01
No	15 (2.8)	10 (5.3)	5 (1.4)	
Yes	524 (97.2)	177 (94.7)	347 (98.6)	

Abbreviation: STI: sexually transmitted infection.

[a]Categories based on self-reported vaccination status. Numbers vary because of missing values.

[b]Based on (parental) country of birth. A women was defined native Dutch if both parents were born in the Netherlands.

[c]High educational level included school of higher general secondary education, preuniversity education, university of applied sciences, and university. Low/middle educational level included all other levels of education.

[d]Vaginal or anal sex.

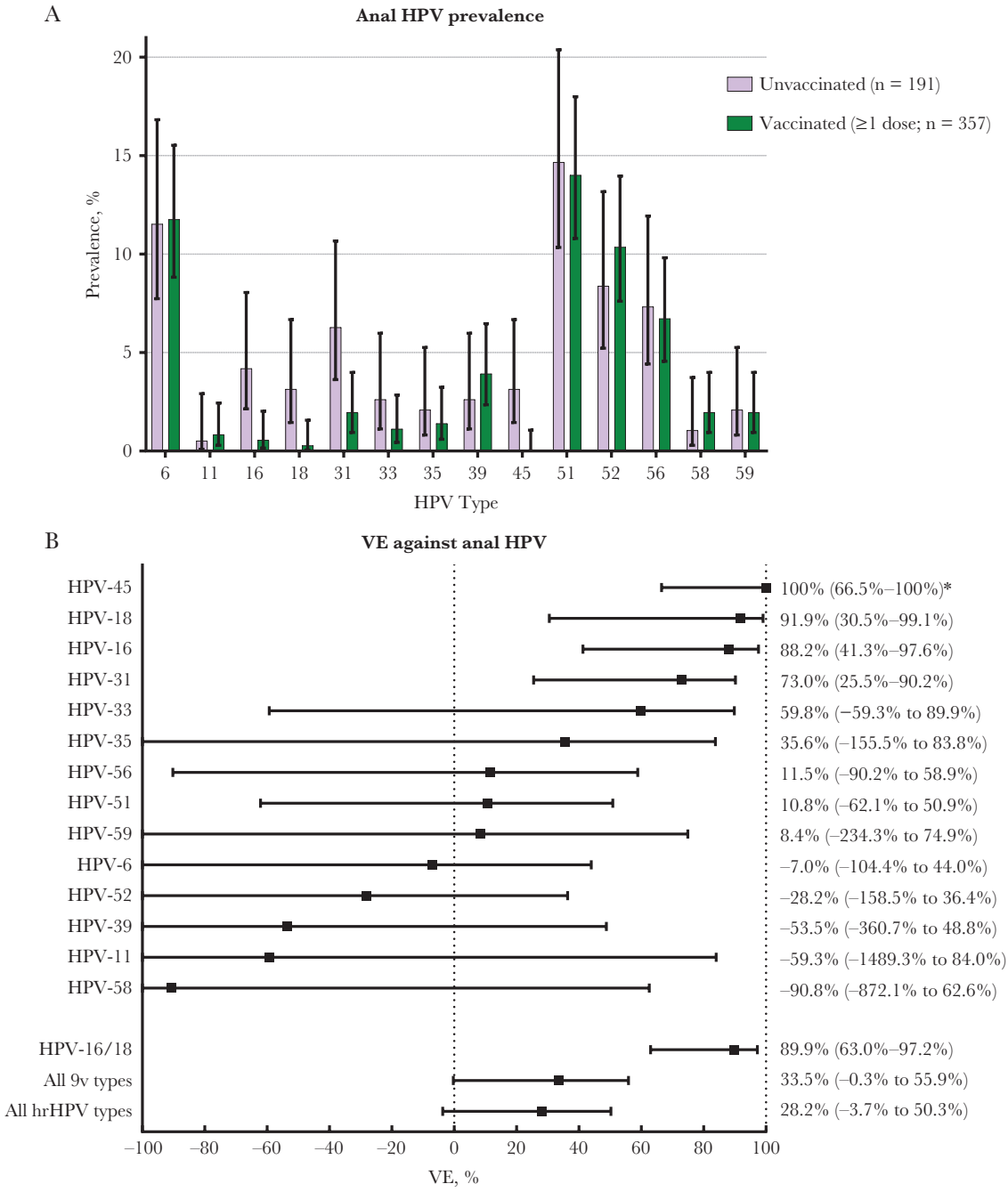

Figure 1. *A,* Anal human papillomavirus (HPV) prevalence by self-reported vaccination status. *B,* Adjusted vaccine effectiveness (VE) against anal HPV for ≥1 dose, with 95% confidence intervals (CIs). All 9-valent (9v) types included all HPV types of the nonavalent vaccine: HPV-6/11/16/18/31/33/45/52/58. All high-risk HPV (hrHPV) types included HPV-16/18/31/33/35/39/45/51/52/56/58/59. Vaccine effectiveness was estimated as (1 – adjusted odds ratio) × 100%. Odds ratios were adjusted for age, education level, history of anal sex, number of sex partners in the past 6 months, sexually transmitted infection–related symptoms, and use of hormonal contraceptives. *Unadjusted 95% CI based on score confidence limits for the odds ratio.

up to 8 years after vaccination. We also demonstrated cross-protection against anal HPV-45 and HPV-31 and a high correlation between anal and cervicovaginal VE. These results confirm that HPV vaccination protects against anal HPV infection among women in a population-based setting, thereby suggesting that the benefits of HPV vaccination will extend to anal cancer prevention.

To our knowledge, this is the first observational study reporting VE of the bivalent HPV vaccine against anal HPV positivity. A strength of our study is the population-based design. A limitation is the differential sexual risk behavior between vaccinated and unvaccinated women who provided an anal swab sample, possibly related to differences in demographics between vaccinated and unvaccinated women in general,

such as education level and migration background [9]. We adjusted for known differences between vaccinated and unvaccinated women who did provide an anal swab sample, but we cannot rule out residual confounding. To mitigate unmeasured confounding, we used mixed models that allow for fixed effects of known risk factors as well as random effects in individual risk for HPV infection.

Another limitation is the self-reported vaccination status. However, we previously showed that self-reported vaccination status agreed excellently with HPV-16 and HPV-18 antibody levels, suggesting limited bias [7]. Moreover, misclassification according to self-reported vaccination status should lead to an underestimation of the effect of vaccination. In addition, the majority of our study population was eligible as part of the catch-up program (84%), meaning that most vaccinated women were between 12 and 16 years old when offered vaccination. Some women in our study population might have acquired anal HPV infection before getting vaccinated, negatively affecting VE [3, 4]. Finally, although we had detailed information on sexual risk behavior, this was not specific for anal sex. For instance, the number of sex partners included anal sex as well as vaginal sex partners.

Our VE against anal HPV-16/18 positivity was comparable to the vaccine efficacy reported against anal HPV-16/18 infection in the RCTs, conducted in women for the bivalent and in men for the quadrivalent vaccine [3–5]. In the only other observational study, the VE against anal HPV-6/11/16/18 positivity was somewhat lower (64%), which could be related to the relatively high anal HPV prevalence before vaccination in that study [6]. Although few effectiveness measures against anal HPV infection are available, the limited data, including ours, suggest an equally high VE against anal as against genital HPV infection. We also observed cross-protection against anal HPV-31 and HPV-45, consistently observed cross-protective types in studies of the bivalent vaccine with regard to cervicovaginal HPV infections [7, 10–13]. Comparable cross-protection is further supported by the high correlation between type-specific VE against anal and cervicovaginal HPV infections in our study.

The mechanism of protection against anal HPV infection is unclear in the current study. Many women who reported no history of anal sex tested positive for anal HPV (34%). This has also been reported elsewhere [14] and resembles anal chlamydia infection patterns [15]. In part, this could be due to underreporting of anal sex, but it is also possible that the relatively high positivity rate for anal HPV is partly explained by autoinoculation from genital HPV infection sites. In these cases, protection against anal HPV infection would be an indirect effect of vaccination, following from the prevention of genital HPV infection. However, the VE against anal HPV-16/18 positivity was equally high (96%) among women who did report a history of anal sex, suggesting undiminished effectiveness with regard to direct protection.

In conclusion, we demonstrated high VE, up to 8 years after vaccination, of the bivalent HPV vaccine against anal HPV infections, which was comparable to prevention of genital infections. The VE was particularly high against anal HPV-16/18 positivity. These findings are promising for anal cancer control, given that nearly 90% of all HPV-related anal cancers are associated with HPV-16/18 [1]. With an increasing incidence of HPV-related anal cancer and a current lack of effective screening opportunities, HPV vaccination provides a tremendous opportunity for anal 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

Acknowledgments. The authors thank Hein Boot (deceased), Elske van Logchem, Naomi van Marm, and Rianne Vriend, for their valuable contributions to the design or execution of the study, and Babette de Geest, who contributed to the data analyses. They also acknowledge the efforts of the sexually transmitted infection clinics within the Public Health Services and hospitals, including all nurses and physicians, and the Medical Microbiologic Laboratories and analysts for storage and testing of the samples.

Members of the Medical Microbiological Laboratories. Certe: D. Adema, R. Buist-Arkema, D. Luijt, S. Meijer, J. Schirm; ETZ Hospital Tilburg: A. Buiting, H. Verbakel, P. van Esch, J. Verweij; Erasmus Medical Center: A. van der Eijk; University Medical Center Utrecht: F. Verduyn Lunel, S. Lakbiach, R. Schuurman; Public Health Laboratory Amsterdam: D. Abma, K. Adams, S. Bruisten, I. Linde, P. Oostvogel, C. Touwen, W. Vermeulen; Maastricht University Medical Center: J. Nelissen, P. Wolffs; Jeroen Bosch Hospital: N. van Duijvendijk, P. Schneeberger; Radboud University Medical Center: M. Dinnissen-van Poppel, W. Melchers; Izore: M. Hooghiemstra, H. Huisman, J. Weel; LabMicTA: F. Bosma, F. Geeraedts, I. Polman; Isala: P. van Goor, M. Wolfhagen; Rijnstate: C. de Mooij, E. van Koolwijk, M. Peters, C. Swanink, R. Tiemessen; Medical Laboratory Dr Stein & College: J. Janssen, M. Pelsers; Canisius Wilhelmina Hospital: W. de Waal.

Members of the Public Health Services. Public Health Service (PHS) Drenthe: G. Aalfs; PHS IJsselland: H. van Buel; PHS Gelderland-Zuid: C. van Bokhoven-Rombouts, P. Cornelissen, M. Kersten, C. van Ruitenbeek, I. Molenaar; University Medical Center Utrecht: E. Doorn; PHS Rotterdam-Rijnmond: H. Götz, M. Illidge, J. Stam, E. Swaders; PHS Groningen: F. Postma; PHS Zuid Limburg: A. M. Niekamp, M. Smit; PHS Fryslân:

D. Bukasa, M. Chirandjilal, T. Taconis; PHS Twente: M. de Graas, I. Hondelink, C. Kampman; PHS Hart voor Brabant: M. van de Pas; PHS Amsterdam: T. Heijman, A. Hogewoning, M. van Rooijen; PHS Gelderland-Midden: F. Neienhuijsen, M. Pelgrim.

Disclaimer. The funders had no role in the study design, data collection and analysis, interpretation of data, decision to publish, or preparation of the manuscript

Financial support. This work was supported by the Ministry of Health, Welfare and Sport, the Netherlands.

Potential conflicts of interest. All authors: No reported conflicts. 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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