The effect of bivalent HPV vaccination against invasive cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3+) in the Netherlands: a population-based linkage study

Marit Middeldorp,[a,b,*] Jesca G. M. Brouwer,[a] Janneke W. Duijster,[a] Mirjam J. Knol,[a] Folkert J. van Kemenade,[c] Albert G. Siebers,[d] Johannes Berkhof,[b] and Hester E. de Melker[a]

[a]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
[b]Department of Epidemiology and Data Science, Amsterdam UMC, Location VUmc, Amsterdam, the Netherlands
[c]Department of Pathology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands
[d]Palga (the Dutch Nationwide Pathology Databank), Houten, the Netherlands

The Lancet Regional Health - Europe 2025;54: 101327

Published Online xxx https://doi.org/10.1016/j.lanepe.2025.101327

Summary

Background The protective effect of HPV vaccination against cervical cancer has been demonstrated in registry linkage studies. The start age of screening in those studies was lower than 25 years. We aimed to estimate the effectiveness of bivalent HPV16/18 vaccination against invasive cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3+) in the Netherlands, where routine screening starts at age 30 years.

Methods We linked the vaccination status of women born in 1993 who were eligible for HPV vaccination at age 16 years with histopathological results recorded until April 1, 2024, in the nationwide pathology databank (Palga). Cumulative risks of invasive cervical cancer and CIN3+ were estimated for fully vaccinated (3 doses or 2 doses ≥150 days apart), partially vaccinated, and unvaccinated women. Cumulative risk ratios (CRRs) were adjusted for differences in screening participation between vaccine groups.

Findings A total of 103,059 women were included, of whom 47,130 were fully vaccinated, 5098 partially vaccinated, and 50,831 unvaccinated. Five cancers (0·011%) were observed in fully vaccinated, two (0·039%) in partially vaccinated, and 42 (0·083%) in unvaccinated women. The CRR for fully vaccinated women compared with unvaccinated women was 0·085 (95% confidence interval 0·025, 0·24) for cancer and 0·19 (0·16, 0·23) for CIN3+. The CRR for partially vaccinated women was 0·52 (0·12, 1·71) for cancer and 0·42 (0·30, 0·57) for CIN3+.

Interpretation The risk of cervical cancer and CIN3+ was strongly reduced in vaccinated women indicating that vaccine protection extends at least until age 30.

Funding The Dutch Ministry of Health, Welfare, and Sport.

Keywords: HPV vaccination; Cervical cancer screening; Effectiveness; Bivalent HPV vaccine; Cervical intraepithelial neoplasia

Introduction

A persistent human papillomavirus (HPV) infection is the established cause of invasive cervical cancer,[1] being the fourth-most common cancer in women worldwide.[2] To eliminate cervical cancer, the importance of HPV vaccination in combination with routine cervical cancer screening and appropriate treatment has been emphasised by the World Health Organization (WHO).[3]

In the Netherlands, bivalent HPV16/18 vaccination with a 3-dose schedule for girls aged 12–13 years was implemented in the National Immunisation Programme (NIP) in 2010. The implementation was preceded by a catch-up campaign in 2009, in which bivalent vaccination was offered to 13–16-year-olds girls (i.e., born between 1993 and 1996). Since its introduction in the Netherlands, the coverage of the HPV vaccination programme has been relatively low, ranging between

*Corresponding author. Centre for Infectious Disease Control, National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, the Netherlands.
E-mail address: marit.middeldorp@rivm.nl (M. Middeldorp).

Research in context

Evidence before this study

We searched PubMed and Google Scholar with the search terms ("Cervical Cancer") AND ("HPV" OR "human papillomavirus") AND ("vaccination"). Articles published in English were searched until January 2, 2025. Studies from Sweden, Denmark, and Scotland were identified linking individual vaccination, screening, and cancer registry data. The start age of screening in these studies was 23–25 years. They showed a strong effectiveness in preventing cervical cancer following the introduction of bivalent and quadrivalent HPV vaccination.

Added value of this study

We observed a very low absolute incidence of cervical cancer in vaccinated women and a much lower incidence of cervical cancer and CIN3+ in women vaccinated at age 16 compared with unvaccinated women, in a setting where routine screening starts at age 30. By linking the vaccination registry to the nationwide pathology databank, we were able to adjust for screening non-attendance in the incidence of cancer and CIN3+ over a 15 year period.

Implications of all the available evidence

Our study found that women vaccinated with the bivalent HPV vaccine had a strongly reduced risk of cervical cancer and CIN3+ in vaccinated women, indicating that vaccine protection extends until at least age 30. This should be considered when determining the start age of screening for women vaccinated at a young age.

46% and 63%.[4] In addition to vaccination, women aged 30–60 years are invited for routine cervical cancer screening every 5–10 years, where the screening interval depends on the women's age and previous test result.[5] Primary screening options include a high-risk (hr) HPV test that can be conducted on either a home-collected sample or a physician-collected sample. Furthermore, some women have a physician-collected sample on medical indication prior to the age of first routine screening (i.e., 30 years).[6] In 2023, women eligible for catch-up HPV vaccination at age 16 (i.e., born in 1993) were invited to participate in routine cervical cancer screening at age 30. This allows us to assess the real-world effectiveness of the bivalent HPV vaccine against invasive cervical cancer.

In this study, we estimated the effectiveness of bivalent HPV vaccination against invasive cervical cancer and cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in the Netherlands. The results presented are the first from a nationwide cohort vaccinated at age 16 and eligible for routine screening for the first time at age 30. This setting is also relevant for countries where screening starts before the age of 30 and a later starting age of screening is being considered. To date, only Italy has increased the start age of screening for vaccinated women from 25 to 30 years.[7] Most other countries are awaiting data on the longevity of vaccine protection before increasing the starting age. Our study can inform local decision-making by providing further evidence on the long-term residual risk of cancer in vaccinated women.

Methods

Study design

For this national linkage study, we selected women registered in the national vaccination registry of the Netherlands (Praeventis). Praeventis is the administrative database from the NIP that includes all children registered as residents in the Netherlands and tracks all vaccines administered within the NIP.[8] The selected women were linked to results of cervical samples and/or tissue sampling recorded in the Dutch nationwide pathology databank (Palga).[9] Deterministic linkage was performed using surname, birthdate, sex, and, if necessary, the first letter of the given name.

Study population

All women registered in Praeventis with birth year 1993 (n = 109,227) were selected. Women were included in the statistical analysis if they were alive and living in the Netherlands at any moment in 2009 (n = 104,661). Women were excluded when vaccinated in a calendar year other than 2009 or 2010, or with an HPV vaccine other than the bivalent vaccine (n = 1602).

A formal sample size calculation was not performed, as we included all women from the first birth cohort eligible for both HPV vaccination and population-based cervical cancer screening in the Netherlands as part of the monitoring of the HPV vaccination programme. The sample size was large enough to detect a 50% reduction in cancer risk in vaccinated women compared to unvaccinated women with 80 percent power (two-sided testing, significance level 0·05).

Data sources and variables

Praeventis contains all relevant information on the HPV vaccination status of each individual in the Netherlands. Women who received the bivalent vaccine were considered fully vaccinated if they received three doses with an interval of 21–150 days between dose 1 and 2 and an interval of at least 120 days between dose 2 and 3, or if two doses were administered at least 150 days apart. They were classified as partially vaccinated if they received one dose, or if they received two or three doses in a schedule that violated the criteria for being fully

vaccinated. Women who did not receive any dose were classified as unvaccinated.

The socioeconomic status (SES), based on a woman's 4-digit postcode of her latest updated address (i.e., around the age of 20 years), was available in Praeventis. This measure of SES is a summary score which reflects financial wealth, education level, and recent labour participation at average household level in 2021 for each postcode (i.e., neighbourhood).[10] The variable for neighbourhood SES was categorised into three groups (high, medium, and low) based on tertiles of its distribution.

Palga contains hrHPV and cytological test results of cervical screening samples and histological results of cervical tissue samples. Cervical tissue samples may be collected after an hrHPV-positive result in the cervical cancer screening programme, where women can choose between self-collection or physician-collection. Cervical tissue samples may also be collected outside the routine screening programme, based on gynaecological complaints (i.e., on medical indication).

From each woman, the hrHPV, cytological, and/or histological test results both within and/or outside the screening programme, along with the participation method in the screening programme were collected from Palga. The hrHPV genotyping results were categorised into the following six categories: positive for HPV types 16 or 18, HPV16/18 along with another hrHPV type, other hrHPV type, hrHPV negative, HPV genotyping result unknown, or hrHPV status unknown. For women with more than one cervical sample, the worst cytological and/or histological test result was considered. hrHPV genotyping results from the period leading up to the diagnosis were considered. If multiple genotyping results were available, the one closest to the diagnosis date was used.

The primary outcomes of this study were histologically confirmed cervical cancer and CIN3+.

Study period

We included cytology results up to February 15, 2024 and histological follow-up after cytology until April 1, 2024. This time window provided sufficient time to obtain a histological confirmation after cytological high-grade squamous intraepithelial lesion (HSIL) as 90% of the women with cytological HSIL had a histological result within 1·5 months. hrHPV testing results were collected until 1 April 2024.

Statistical analysis

Descriptive analyses were performed for fully vaccinated, partially vaccinated, and unvaccinated women. We calculated the proportion of women with available test results (hrHPV, cytological, and/or histological result) both within and/or outside the screening programme, the proportion of women choosing self-collection, and the proportion of HPV-positive test results among women in the screening programme. Furthermore, we reported the number of histologically confirmed cervical cancers, CIN3, and CIN2. Among the cervical cancer and CIN3+ cases detected both within and outside the screening programme, the proportions of hrHPV genotyping results were calculated.

Cumulative risks of cervical cancer and CIN3+ were calculated for each vaccine group (fully vaccinated, partially vaccinated, and unvaccinated). Women were included in the denominator of the risk estimate, irrespective of whether they had a result in Palga. Crude cumulative risks for end-points cervical cancer and CIN3+ were also calculated for each vaccine group by age of diagnosis (<25 years, 25–29 years, and 30–31 years).

To account for the difference in routine screening participation rate per vaccination group, we calculated the adjusted cumulative cancer (and CIN3+) risk per vaccination group by summing the cumulative risk detected outside the screening programme and the cumulative risk detected within the screening programme, where we divided the latter risk by the screening participation percentage in the vaccination group. Jeffrey's intervals were calculated around the crude and adjusted risks.[11]

Women with CIN grade 3 or worse detected outside the screening programme were excluded from the denominator when calculating the cumulative risk detected within the screening programme. The cumulative risk ratios (CRRs) were calculated as the cumulative risk in either fully or partially vaccinated women divided by the cumulative risk in unvaccinated women. CRRs were accompanied by 95% confidence intervals (95% CIs).

Crude CRRs estimates were additionally stratified by neighbourhood SES, and the SES-stratified estimates were pooled using the Mantel–Haenszel method.

A sensitivity analysis was performed with a less strict approach regarding vaccination status. This analysis additionally included women who were vaccinated in calendar years other than 2009 or 2010 or who received an HPV vaccine other than the bivalent vaccine (n = 1602).

All analyses were performed using R (version 4.4.0).

Ethics approval

Approval for the study was obtained from Praeventis and Palga. The study was exempt from ethical approval as data were gathered retrospectively and individuals were not subjected to actions or rules of conduct. The report of this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12]

Role of the funding source

This study was funded by the Dutch Ministry of Health, Welfare, and Sport. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Results

Characteristics of the study population

A total of 103,059 women were included in the analyses (Figure S1). Of these, 47,130 (45·7%) were fully vaccinated with either two doses (2·0%) or three doses (98·0%), 5098 (5·0%) were partially vaccinated, and 50,831 (49·3%) were unvaccinated (Table 1). The percentage of women living in a neighbourhood with a low SES was lowest for fully vaccinated women (n = 23,322; 49·5%) and highest for partially vaccinated women

	Fully vaccinated	Partially vaccinated	Unvaccinated
Number of women	47,130 (45·7%)	5098 (5·0%)	50,831 (49·3%)
Number of doses			
3	46,190 (98·0%)	11 (0·22%)	0 (0·0%)
2	940 (2·0%)	2837 (55·6%)	0 (0·0%)
1	0 (0·0%)	2250 (44·1%)	0 (0·0%)
0	0 (0·0%)	0 (0·0%)	50,831 (100·0%)
Neighbourhood socioeconomic status			
High	9391 (19·9%)	749 (14·7%)	9248 (18·2%)
Medium	14,277 (30·3%)	1338 (26·2%)	14,609 (28·8%)
Low	23,322 (49·5%)	2992 (58·7%)	26,813 (52·8%)
Unknown	140 (0·30%)	19 (0·37%)	161 (0·32%)
Cervical cancer screening participation rate	27,692 (58·8%)	2207 (43·3%)	22,478 (44·2%)
Origin of cervical sample			
Within screening programme only	20,618 (43·7%)	1492 (29·3%)	15,964 (31·4%)
Outside screening programme only	4672 (9·9%)	740 (14·5%)	5652 (11·1%)
Both within and outside screening programme	7074 (15·0%)	715 (14·0%)	6514 (12·8%)
No cervical sample	14,766 (31·3%)	2151 (42·2%)	22,701 (44·7%)
Participation method in screening programme			
Self-sampling kit at home	16,492 (59·6%)	1323 (59·9%)	13,361 (59·4%)
Smear at the general practitioner	11,200 (40·4%)	884 (40·1%)	9117 (40·6%)
hrHPV genotyping result within screening programme			
16|18	30 (0·11%)	12 (0·54%)	821 (3·7%)
16|18 and other hrHPV type[a]	17 (0·06%)	8 (0·36%)	763 (3·4%)
Other hrHPV type[a]	3977 (14·4%)	354 (16·0%)	2773 (12·3%)
hrHPV negative	23,272 (84·0%)	1781 (80·7%)	17,684 (78·7%)
HPV genotyping result unknown[b]	370 (1·3%)	50 (2·3%)	441 (1·8%)
hrHPV status unknown[c]	26 (0·09%)	2 (0·09%)	26 (0·12%)
hrHPV genotyping result outside screening programme			
16|18	8 (0·07%)	3 (0·21%)	354 (2·9%)
16|18 and other hrHPV type[a]	6 (0·05%)	4 (0·27%)	380 (3·1%)
Other hrHPV type[a]	629 (5·4%)	80 (5·5%)	582 (4·8%)
hrHPV negative	2861 (24·4%)	337 (23·2%)	2774 (22·8%)
HPV genotyping result unknown[b]	1084 (9·2%)	181 (12·4%)	1562 (12·8%)
hrHPV status unknown[c]	7158 (60·9%)	850 (58·4%)	6514 (53·5%)
Number of cervical cancers			
Within screening programme	0 (0·0%)	1 (50·0%)	17 (40·5%)
Outside screening programme	5 (100·0%)	1 (50·0%)	25 (59·5%)
Total	5	2	42
Number of CIN3			
Within screening programme	71 (42·3%)	15 (50·0%)	348 (45·7%)
Outside screening programme	95 (57·2%)	15 (50·0%)	413 (54·3%)
Total	166	30	761
Number of CIN2			
Within screening programme	90 (30·6%)	8 (16·0%)	234 (35·9%)
Outside screening programme	204 (69·4)	42 (84·0%)	417 (64·1%)
Total	294	50	651

Abbreviations: CIN3: cervical intraepithelial neoplasia grade 3; CIN2: cervical intraepithelial neoplasia grade 2. [a]Other hrHPV types include HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. [b]hrHPV positive women without hrHPV genotyping result. [c]Samples not tested for presence of hrHPV DNA.

Table 1: **Characteristics of the study population.**

(n = 2992; 58·7%). A higher participation rate in the routine cervical cancer screening programme was observed among fully vaccinated women (n = 27,692; 58·8%) than among partially vaccinated women (n = 2207; 43·3%) and unvaccinated women (n = 22,478; 44·2%). The percentage of women with test results available outside the screening programme was similar for fully vaccinated women and unvaccinated women (n = 11,746; 24·9% and n = 11,266; 23·9%, respectively) and slightly higher for partially vaccinated women (n = 1455; 28·5%). Additionally, 31·3% (n = 14,766) of the fully vaccinated women, 42·2% (n = 2151) of the partially vaccinated women, and 44·7% (n = 22,701) of the unvaccinated women never had a cervical screening or tissue sample.

For women who participated in the routine screening programme, approximately 60% (n = 31,176) used a self-sampling kit at home, while 40% (n = 21,201) visited their general practitioner for a cervical scrape (Table 1). 84·0% (n = 23,272) of fully vaccinated women, 80·7% (n = 1781) of partially vaccinated women, and 78·7% (n = 17,684) of unvaccinated women had a negative hrHPV test in the cervical screening programme. HPV16/18 positivity was highest in unvaccinated women, but also higher in partially vaccinated women than in fully vaccinated women.

The majority (n = 14,522; 57·6%) of women with a cervical sample collected outside the screening programme had an unknown hrHPV status as their sample was not tested for presence of hrHPV DNA.

Cervical cancer and cervical intraepithelial neoplasia

Cumulative risks and risk ratios

In total, 49 women were diagnosed with cervical cancer. Of these, five were fully vaccinated (cumulative risk: 0·011%, 95% CI 0·0040, 0·024), two were partially vaccinated (0·039%, 95% CI 0·0082, 0·13), and 42 were unvaccinated (0·083%, 95% CI 0·060, 0·11) (Tables 1 and 2). The five cervical cancers diagnosed in fully vaccinated women were all identified outside the screening programme. In partially vaccinated women, one cancer was diagnosed in the screening programme and one outside the screening programme. In unvaccinated women, 17 (40·5%) of the cancers were detected in the screening programme and 25 (59·5%) were detected outside the screening programme. Also within each age group at the time of diagnosis, unvaccinated women had higher risks of cervical cancer and CIN3+ compared to vaccinated women (Figs. 1 and 2).

For women fully vaccinated at 16 years of age with the bivalent HPV vaccine, the CRR for cervical cancer was 0·13 (95% CI 0·037, 0·39) (Table 2). When accounting for the differences in screening participation, the CRR was 0·085 (95% CI 0·025, 0·24). For partially vaccinated women, the adjusted CRR for cancer was 0·52 (95% CI 0·12, 1·71).

In total, 957 women were diagnosed with CIN3 (Table 1). Of them, 166 were fully vaccinated, 30 were partially vaccinated, and 761 were unvaccinated. The crude and adjusted CRRs for CIN3+ among fully vaccinated women compared to unvaccinated women were 0·23 (95% CI 0·18, 0·28) and 0·19 (95% CI 0·16, 0·23), respectively (Table 2). The adjusted CRR for CIN3+ among partially vaccinated women compared to unvaccinated women was 0·42 (95% CI 0·30, 0·57).

Furthermore, 995 women were diagnosed with CIN2 (Table 1). Of these, 294 were fully vaccinated, 50 were partially vaccinated, and 651 were unvaccinated. Table 1 shows the number of CIN3 and CIN2 detected within and outside the screening programme.

The crude CRRs adjusted by neighbourhood SES demonstrated similar estimates for fully vaccinated women against cervical cancer (0·13, 95% CI 0·039, 0·32) and CIN3+ (0·23, 95% CI 0·19, 0·27) when compared to the crude effectiveness estimates from the main analyses reported in Table 2.

hrHPV genotyping results

In the screening programme, one partially vaccinated woman diagnosed with cervical cancer was positive for HPV16/18 along with another hrHPV type (Table S1). Among unvaccinated women diagnosed with cervical cancer in the screening programme, 9 (52·9%) were positive for HPV16/18 and 5 (29·4%) were positive for HPV16/18 along with another hrHPV type.

Among fully vaccinated women diagnosed with CIN3+ in the screening programme, 3 (4·2%) were

	Number of cervical cancer	Risk, % (95% CI)	Crude CRR (95% CI)	Adjusted[a] CRR (95% CI)	Number of CIN3+	Risk, % (95% CI)	Crude CRR (95% CI)	Adjusted[a] CRR (95% CI)
Fully vaccinated (n = 47,130)	5	0·011 (0·0040, 0·024)	0·13 (0·037, 0·39)	0·085 (0·025, 0·24)	171	0·36 (0·31, 0·42)	0·23 (0·18, 0·28)	0·19 (0·16, 0·23)
Partially vaccinated (n = 5098)	2	0·039 (0·0082, 0·13)	0·47 (0·074, 2·08)	0·52 (0·12, 1·71)	32	0·63 (0·44, 0·87)	0·40 (0·26, 0·59)	0·42 (0·30, 0·57)
Unvaccinated (n = 50,831)	42	0·083 (0·060, 0·11)	Ref.	Ref.	803	1·58 (1·48, 1·69)	Ref.	Ref.

Abbreviations: n: number of women; CIN3+: cervical intraepithelial neoplasia grade 3 or worse; Risk: crude cumulative risk; CRR: cumulative risk ratio; CI: confidence interval; Ref.: reference category.
[a]Adjusted for differences in cervical cancer screening participation by vaccination status.

Table 2: **Cumulative risks of cervical cancer and cervical intraepithelial neoplasia grade 3 or worse (CIN3+) by vaccination status with corresponding cumulative risk ratios.**

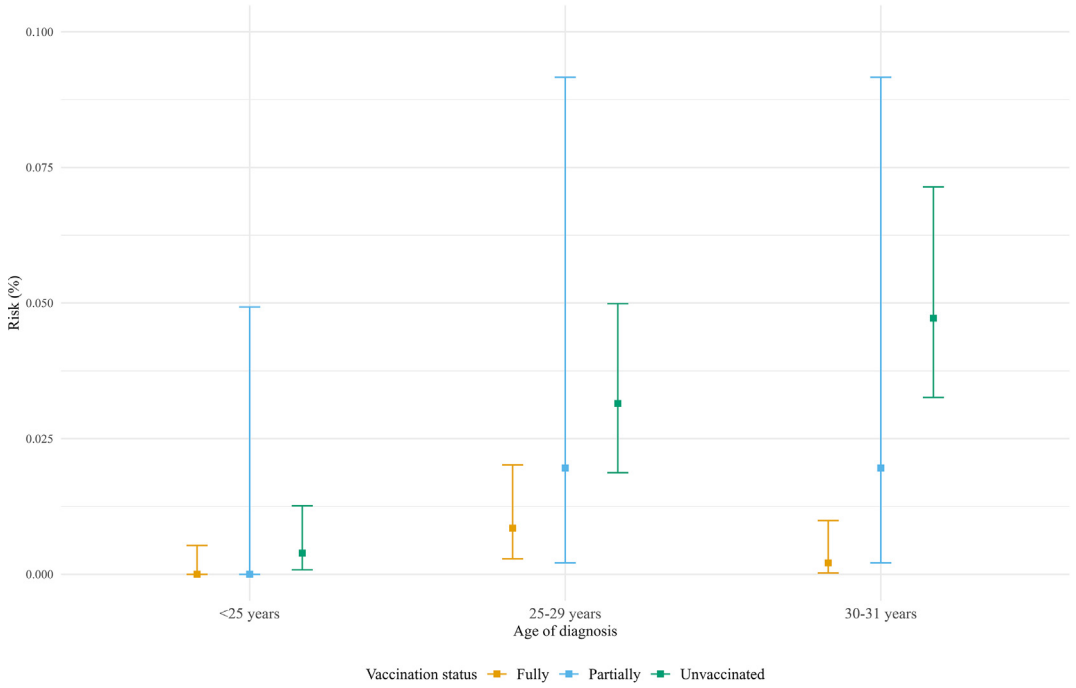

Fig. 1: **Risk of having cervical cancer diagnosed within the specified age window stratified by vaccination status**.

positive for at least HPV16 or HPV18, while 67 (94·4%) were positive for an hrHPV type other than HPV16 or HPV18 (Table S1). For partially vaccinated women, these numbers were 5 (31·3%) and 11 (68·8%), respectively. For unvaccinated women, these numbers were 284 (77·8%) and 76 (20·8%), respectively.

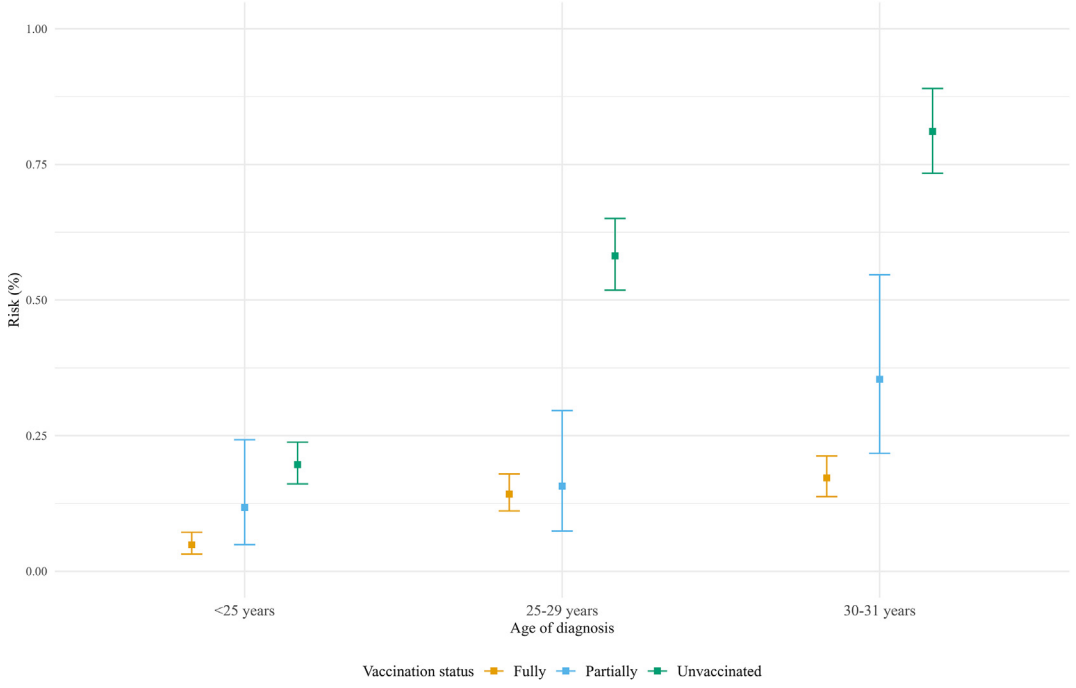

Fig. 2: **Risk of having cervical intraepithelial neoplasia grade 3 or worse (CIN3+) diagnosed within the specified age window stratified by vaccination status**.

Sensitivity analysis

In the sensitivity analysis, all women who were eligible for HPV vaccination in 2009 were included (n = 104,661). The estimates were similar to those in the main analysis for both cervical cancer and CIN3+ (Table S2). The adjusted CRR for cervical cancer among fully vaccinated women compared to unvaccinated women was 0·082 (95% CI 0·025, 0·23). For CIN3+, the adjusted CRR was estimated at 0·20 (95% CI 0·16, 0·23). For partially vaccinated women, the adjusted CRRs were 0·49 (95% CI 0·12, 1·63) against cervical cancer and 0·40 (95% CI 0·29, 0·55) against CIN3+.

Discussion

With this national linkage study, we showed that bivalent HPV vaccination at 16 years of age substantially reduces the risk of invasive cervical cancer and CIN3+ when comparing fully vaccinated women to unvaccinated women. For partially vaccinated women, the risk reduction for CIN3+ was lower than for fully vaccinated women and the risk reduction for cancer was not significant, probably due to the small number of partially vaccinated women which increases the uncertainty around the point estimate.

The observed crude effectiveness of 87% (CRR: 0·13) against cervical cancer is consistent with previous research from Scotland, which reported an effectiveness of 86% among women vaccinated at 14–16 years of age with the bivalent HPV vaccine.[13] In Sweden and Denmark, comparable effectiveness estimates were observed among women vaccinated with the quadrivalent vaccine before 17 years of age.[14,15] In England, an observational study without individual linkage between the vaccine and cancer registry reported a slightly lower effect (62%) among women who were offered bivalent vaccination at 14–16 years of age.[16]

The lower cervical cancer screening participation rate among unvaccinated women in our study has also been observed in other countries.[17–19] A higher screening participation among vaccinated women increases the probability of detecting an asymptomatic cervical cancer in this group and may lead to a negatively biased effectiveness estimate.[15] After accounting for the difference in screening participation rate by vaccination status, the effectiveness against cervical cancer increased to 92% (CRR: 0·085) for fully vaccinated women in our study. Our finding of a slightly lower protective effect against CIN3+ compared to invasive cancer aligns with previous studies from Denmark,[14,20] and might be due to the stronger association between cervical cancer and HPV types 16 and 18 than between CIN3 and these HPV types.[21] A Norwegian study found a reduced risk of HPV16/18-associated CIN3+ over time among screened women who were offered vaccination at ages 21–26, but not for CIN3+ associated with other hrHPV types.[22] In our study, a high effectiveness against CIN3+ was still observed for fully vaccinated women and further increased after adjusting for differences in screening participation. In England and Sweden, the effect estimates against CIN3+ were similar as in our study.[16,23] In Australia, the quadrivalent vaccine demonstrated a slightly lower effect (57%).[24]

In the Netherlands, the likelihood of detecting CIN3+ is highest at ages 30–31 because routine screening starts at age 30. We observed a comparable risk of CIN3+ both before age 30 and at ages 30–31 among vaccinated women, suggesting that vaccine protection extends at least until age 30. This information needs to be taken into account when determining the optimal screening start age for vaccinated women.

In our study, we observed five cases of cervical cancer in women fully vaccinated at 16 years of age. Globally, HPV types 16 and 18 are responsible for approximately 75% of cervical cancer cases, and HPV types 31, 33, and 45 account for an additional 11% of cervical cancers.[25] Consequently, even in the presence of cross-protection,[26] fully vaccinated women can still develop cervical cancer due to hrHPV types that are not targeted by the vaccine. This underscores that cervical cancer screening still offers health gains, also to those who are fully vaccinated, potentially through customised screening strategies for vaccinated women to prevent overtreatment.[27]

A considerable number of women in our study population did not make use of any of the cervical cancer prevention methods, i.e., vaccination and screening. These women are at increased risk of developing cervical cancer. They may still benefit from the indirect effects of HPV vaccination that we observed in the Netherlands,[28] although the herd effect is expected to be limited for the first vaccinated cohort and will become stronger for future cohorts. In addition, switching to gender-neutral vaccination may become beneficial for unvaccinated women as well since the expected herd effect is expected to increase.[27,29]

Cervical samples collected following a medical consultation, rather than as part of the screening programme, creates the potential to interrupt the progression of cervical cancer when pre-cancerous lesions at a pre-screening age are detected and treated. Consequently, women with pathology results from medically initiated cervical samples may contribute to a lower incidence of cervical cancer. In our study, the percentage of women with a pathology results of a medically initiated cervical sample (i.e., outside the screening programme) was comparable for vaccinated and unvaccinated women. Therefore, it is unlikely that the observed results are biased by a difference in screening outside the programme between vaccinated and unvaccinated women.

We observed lower effectiveness in the partially vaccinated group compared with the fully vaccinated group. One possible explanation is that partially

vaccinated women have a higher risk of acquiring HPV infection than fully vaccinated women. This effect may translate into lower effectiveness, as women in our population were vaccinated at the age of 16 years and pre-vaccination exposure to HPV cannot be excluded. Although we did not collect individual data on risk behaviour, partially vaccinated women had a lower cervical screening uptake, lower neighbourhood SES, higher HPV16/18 prevalence at routine screening, and a slightly higher HPV prevalence for other genotypes than fully vaccinated women. This may be associated with lower levels of health-protective or higher sexual risk behaviour.[30] A second possible explanation is that completing the full vaccination schedule gives better protection against cervical cancer and CIN3+ than partial vaccination. Our study is consistent with a recent Scottish linkage study which reported a slightly higher risk of cancer after partial vaccination with the bivalent vaccine than after full vaccination at age 14 years or older.[13] A recent Swedish linkage study also observed comparable vaccine effectiveness against CIN2+ for one, two, and three doses of the quadrivalent vaccine when given before the age of 15, but slightly higher risks for one dose compared to three doses in older age groups.[31] In addition, two ongoing randomised controlled trials indicate that one dose provides stable high immunogenicity levels over five years of follow-up, although geometric mean concentration levels (GMCs) were slightly lower with a single dose than with two doses. A strong protection against HPV infections over three years of follow-up was observed.[32–36] In summary, several studies suggest that a single-dose vaccination schedule is highly effective, but close monitoring of current and future vaccinated cohorts remains important to consider whether specific age groups might benefit from more than one dose to achieve optimal protection against cancer and CIN3.

The cohort included in this study consisted of women eligible for bivalent HPV vaccination at 16 years of age (catch-up vaccination). Consequently, it is possible that women were exposed to HPV before vaccination, given that the median age of sexual debut among female adolescents in the Netherlands in 2012 was 16·8 years.[37] Other studies found that a higher effectiveness against cervical cancer is associated with a younger age of HPV vaccination for both the bivalent and quadrivalent vaccine.[13–16] Therefore, we may in the future observe an even higher effectiveness against cervical cancer in the Netherlands, as the age of invitation for HPV vaccination was lowered to 12 years in 2014 and further reduced to 9 years in 2022. Moreover, it has been suggested that the number of cervical cancer cases will decrease across the population due to more pronounced indirect effects among the unvaccinated population if more birth cohorts receive vaccination.[14,28]

A strength of our study is that we were able to link national databases on vaccination, screening and cancer data which enables the assessment of the long-term effectiveness of vaccination. Additionally, by using the information from the national vaccination registry, the risk of misclassification regarding the vaccination status was minimised. However, our study also has some limitations. First, we were only able to adjust for screening attendance and neighbourhood SES. We were unable to adjust for other variables that potentially confound the association between HPV vaccination and the risk of cervical cancer such as sexual behaviour, exposure to HPV before vaccination, and smoking. However, it is reassuring that the prevalence of non-vaccine hrHPV types was similar in fully vaccinated and unvaccinated women, suggesting similar HPV exposure in the two groups. A second limitation is the dataset's incompleteness regarding emigration and death records. Emigration and death records are regularly updated in Praeventis until the individual is not eligible for the NIP anymore, i.e., up to 20 years of age. This incompleteness may have affected the results if there are substantial differences in emigration and/or death after the age of 20 between vaccinated and unvaccinated women, which is unlikely as indicated by Schurink-van 't Klooster et al.[6] A third limitation is the unavailability of genotype specific results for non-vaccine hrHPV types. However, a recent change in the choice of the primary HPV DNA test in the screening programme that allows further stratification of non16/18 infections (BD Onclarity, BD and Company, Frankin Lakes, NJ), will likely help provide more accurate information about the cross-protective effect of the bivalent vaccine in the coming years. A fourth limitation is that follow-up data are incomplete for hrHPV-positive women in the screening programme who were invited for repeat cytology after one year. This includes women with low grade abnormal cytology (ASCUS/LSIL) who are negative for HPV16/18 and women with normal cytology.[5] The effect of vaccination, expressed as a cumulative risk ratio, may be overestimated because of incomplete follow-up of women with HPV16/18-negative ASCUS/LSIL, although the proportion of HPV16/18-negative ASCUS/LSIL was similar in fully vaccinated, partially vaccinated, and unvaccinated women.

In conclusion, we observed that bivalent HPV vaccination administered at 16 years of age was associated with a strongly reduced risk of cervical cancer and CIN3+. The extent of protection against cervical cancer for partially vaccinated women could not be determined with certainty due to the low number of cases. We will continue to monitor the effectiveness of HPV vaccination in this birth cohort and in subsequent cohorts. As more individuals eligible for HPV vaccination enter the cervical cancer screening programme at age 30,

evidence of the long-term effectiveness of the vaccine in preventing cervical cancer, including indirect protective effects in unvaccinated women, will accumulate.

Contributors

HEdM, JGMB, JB, AGS, and MM conceptualised the study. AGS and FJK contributed to data collection. MM and JGMB performed the statistical analysis under the supervision of JB, MK, and HEdM. MM prepared the original draft of the paper. All authors critically reviewed and edited the manuscript and approved the final version. MM and JGMB verified the data. MM, JGMB, JD, and HEdM had full access to raw data in the study. HEdM had final responsibility for the decision to submit for publication.

Data sharing statement

Aggregated data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available, as this could compromise the privacy of the participants.

Declaration of interests

JB was supported by the European Union Horizon 2020 Framework Programme for Research and Innovation, RISCC project (grant number 847845), and received support for attending Eurogin conferences (Dusseldorf 2022, Bilbao 2023, Stockholm 2024, and Porto 2025) and a RISCC meeting (Barcelona 2024). All other authors declare no conflicts of interest.

Acknowledgements

This study was funded by the Dutch Ministry of Health, Welfare, and Sport.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101327.

References

1 Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12–19.
2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
3 World Health Organization, WHO. Global strategy to accelerate the elimination of cervical cancer as a public health problem. https://iris.who.int/handle/10665/336583; 2020. Accessed September 3, 2024.
4 Pluijmaekers A, de Melker H. *The National Immunisation Programme in The Netherlands. Surveillance and Developments in 2022–2023*. Bilthoven, the Netherlands: RIVM; 2023.
5 National Institute for Public Health and the Environment, RIVM. Cervical cancer screening programme. https://www.rivm.nl/en/cervical-cancer-screening-programme; 2024. Accessed September 3, 2024.
6 Schurink-van 't Klooster TM, Siebers AG, Hoes J, et al. Early effect of bivalent human papillomavirus vaccination on cytology outcomes in cervical samples among young women in the Netherlands. *Cancer Med*. 2023;12(10):11786–11794.
7 Martello G, Gori S, Frayle H, Franceschi S, Zorzi M, Del Mistro A. Acceptability of deferring the start of cervical cancer screening to age 30 for women vaccinated against human papillomavirus. *Prev Med Rep*. 2023;36:102438.
8 Van Lier A, Oomen P, de Hoogh P, et al. Praeventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. *Euro Surveill*. 2012;17(17):20153.
9 Casparie M, Tiebosch A, Burger G, et al. Pathology databanking and biobanking in the Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Anal Cell Pathol*. 2007;29(1):19–24.
10 Statistics Netherlands, CBS. Socioeconomic status by four-digit zip code. https://www.cbs.nl/nl-nl/maatwerk/2024/24/sociaal-economische-status-per-viercijferige-postcode; 2024. Accessed September 13, 2024.
11 Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci*. 2001;16(2):101–133.
12 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.
13 Palmer TJ, Kavanagh K, Cuschieri K, et al. Invasive cervical cancer incidence following bivalent human papillomavirus vaccination: a population-based observational study of age at immunization, dose, and deprivation. *J Natl Cancer Inst*. 2024;116(6):857–865.
14 Kjaer SK, Dehlendorff C, Belmonte F, Baandrup L. Real-world effectiveness of human papillomavirus vaccination against cervical cancer. *J Natl Cancer Inst*. 2021;113(10):1329–1335.
15 Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 2020;383(14):1340–1348.
16 Falcaro M, Castañon A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *Lancet*. 2021;398(10316):2084–2092.
17 Kreusch T, Wang J, Sparén P, Sundström K. Opportunistic HPV vaccination at age 16–23 and cervical screening attendance in Sweden: a national register-based cohort study. *BMJ Open*. 2018;8(10):e024477.
18 Beer H, Hibbitts S, Brophy S, Rahman M, Waller J, Paranjothy S. Does the HPV vaccination programme have implications for cervical screening programmes in the UK? *Vaccine*. 2014;32(16):1828–1833.
19 Australian Institute of Health and Welfare. *Analysis of Cervical Cancer and Abnormality Outcomes in an Era of Cervical Screening and HPV Vaccination in Australia*. Canberra: AIHW; 2019. Cancer series no. 126. Cat. no. CAN 129.
20 Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: a Danish nationwide cohort study. *Clin Infect Dis*. 2020;70(4):608–614.
21 Dovey de la Cour C, Guleria S, Nygård M, et al. Human papillomavirus types in cervical high-grade lesions or cancer among Nordic women-Potential for prevention. *Cancer Med*. 2019;8(2):839–849.
22 Jørgensen AS, Simonsen GS, Sørbye SW. Impact of HPV catch-up vaccination on high-grade cervical lesions (CIN2+) among women aged 26–30 in Northern Norway. *Vaccines (Basel)*. 2025;13(1):96.
23 Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study. *Int J Cancer*. 2016;138(12):2867–2874.
24 Brotherton JM, Budd A, Rompotis C, et al. Is one dose of human papillomavirus vaccine as effective as three?: a national cohort analysis. *Papillomavirus Res*. 2019;8:100177.
25 Wei F, Georges D, Man I, Baussano I, Clifford GM. Causal attribution of human papillomavirus genotypes to invasive cervical cancer worldwide: a systematic analysis of the global literature. *Lancet*. 2024;404(10451):435–444.
26 Hoes J, King AJ, Berkhof J, de Melker HE. High vaccine effectiveness persists for ten years after HPV16/18 vaccination among young Dutch women. *Vaccine*. 2023;41(2):285–289.
27 Lehtinen M, Elfström M, Vänskä S, Dillner J. Elimination of cervical cancer by refined vaccination and screening. *Int J Cancer*. 2025;156(4):886–888.
28 Middeldorp M, Duijster JW, Knol MJ, et al. The indirect effect of the bivalent human papillomavirus vaccination program: an observational cohort study. *BMC Med*. 2025 (in press).
29 Lehtinen M, Luostarinen T, Vänskä S, et al. Gender-neutral vaccination provides improved control of human papillomavirus types 18/31/33/35 through herd immunity: results of a community randomized trial (III). *Int J Cancer*. 2018;143(9):2299–2310.
30 Malagón T, Joumier V, Boily MC, Van de Velde N, Drolet M, Brisson M. The impact of differential uptake of HPV vaccine by sexual risks on health inequalities: a model-based analysis. *Vaccine*. 2013;31(13):1740–1747.
31 Wu S, Ploner A, Alsina AMA, Deng Y, Schollin LA, Lei J. Effectiveness of quadrivalent human papillomavirus vaccination against high-grade cervical lesions by age and doses: a population-based cohort study. *Lancet Reg Health Eur*. 2025;49:101178.
32 Barnabas RV, Brown ER, Onono MA, et al. Efficacy of single-dose human papillomavirus vaccination among young African women. *NEJM Evid*. 2022;1(5):EVIDoa2100056.
33 Baisley K, Kemp TJ, Mugo NR, et al. Comparing one dose of HPV vaccine in girls aged 9–14 years in Tanzania (DoRIS) with one dose

in young women aged 15–20 years in Kenya (KEN SHE): an immunobridging analysis of randomised controlled trials. *Lancet Global Health*. 2024;12(3):e491–e499.
34 Barnabas RV, Brown ER, Onono MA, et al. Durability of single-dose HPV vaccination in young Kenyan women: randomized controlled trial 3-year results. *Nat Med*. 2023;29(12):3224–3232.
35 Watson-Jones D, Changalucha J, Maxwell C, et al. Durability of immunogenicity at 5 years after a single dose of human papillomavirus vaccine compared with two doses in Tanzanian girls aged 9–14 years: results of the long-term extension of the DoRIS randomised trial. *Lancet Global Health*. 2025;13(2):e319–e328.
36 Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. *Lancet Global Health*. 2022;10(10):e1473–e1484.
37 Cense M. *Ze weten wel wat ze moeten typen, maar niet wat ze moeten zeggen. Verklaringen voor een latere seksuele start*. Utrecht: Rutgers; 2018.