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Original Article

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HPV vaccination status and effectiveness in Korean women with HPV16/18 infection (2010–2021): a retrospective study

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ABSTRACT

Objective: To evaluate human papillomavirus (HPV) vaccine effectiveness in a cohort of Korean women infected with HPV.
Methods: From 2010 to 2021, Korean women aged 20–60 years who diagnosed HPV-positive atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion were recruited from 6 hospitals. HPV vaccine effectiveness was estimated by observing the differences in pathological and clinical information and experimental results—prevalence, viral load (VL), physical state (PS), and HPV16/18 infection duration—between the vaccinated and unvaccinated groups.
Results: HPV16/18 prevalence declined from 18.5% to 11.8% as vaccination rates increased from 14.3% to 60.7% in the 1,757 registered cohort women. DNA analysis from 96 samples collected from the participants, indicated that HPV vaccination reduced HPV16 VL by 6 times and increased E2/E6 ratio for both HPV16 and HPV18 by 1.4 and 5 times, respectively. The HPV16 infection rate—lasting more than 18 months from 31.0% to 21.6%—and the HPV18 infection rate—lasting more than 12 and less than 24 months from 35.5% to 21.1%—were reduced by vaccination. We found VL and the infection duration to be directly proportional. Moreover, HPV vaccination reduced not only the VL to 1/4 in both the persistence and clearance groups but also the persistence rate from 90% (27/30) to 70.6% (12/17) in HPV16.
Conclusion: HPV vaccination reduced the prevalence and duration of infection and kept the PS in an episomal form for both HPV16 and HPV18. The tendency of persistence VL to be higher than clearance in the unvaccinated group implies that the vaccine's effect of reducing VL in HPV16 may lower the risk of progression to cervical cancer by shortening the infection duration.

Keywords: Human Papillomavirus Vaccine; Prevalence; Viral Load; Duration of Infection

Synopsis

The HPV vaccine was first introduced in 2007; research on its efficacy in Korean women is still lacking. The vaccine efficacy was evaluated in 1,757 Korean women infected with HPV from 2010 to 2021. The increased vaccination rate reduced HPV prevalence and viral load.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

In South Korean women aged 15–44 years, cervical cancer is a leading cause of mortality related to female cancer and female cancer, ranked fourth and third, respectively [1]. More than 95% of cervical cancer cases are caused by human papillomavirus (HPV) infection; at least 70% of cervical cancer cases are due to HPV types 16 and 18 [2]. Although almost all HPV infections spontaneously clear within a few months to 2 years [3], a few persistent infections can develop into high-grade precancerous lesions [4].

Several studies have suggested viral load (VL) and physical state (PS), particularly for high-risk HPV, as risk factors for cervical malignancy. For instance, in Indian women aged >30 years infected with monotypic HPV16, VL and integration were found to increase with disease severity (low-grade squamous intraepithelial lesion [LSIL]<high-grade squamous intraepithelial lesions [HSIL]<invasive cancer) [5]. Albeit with some variations, a high VL was observed in invasive carcinoma compared with that in other conditions (normal and cervical intraepithelial neoplasia [CIN] 1–3), and the E2/E6 ratio was higher in controls (normal and CIN1) than in cases (CIN2, CIN3, and invasive carcinoma) (E2/E6≥0.92 for episomal, 0<E2/E6<0.92 for mixed, and E2/E6=0 for integrated) [6]. Moreover, HPV16/18 VL has been recommended as a marker for persistent infection [7]. In this study, VL was higher in participants with persistent infections than in participants with clearing infections in a Dutch HPV cohort.

The Korea Ministry of Food and Drug Safety (MFDS) approved the bivalent HPV vaccine Cervarix (types 16 and 18) and the quadrivalent vaccine Gardasil (types 6, 11, 16, and 18) in 2008 and 2007, respectively [8]. These 2 virus-like particle vaccines mimic the virus and express recombinant L1 capsids without being infectious [9]. HPV vaccines have been shown to reduce the prevalence of HPV16 and HPV18 in women aged 18–24 years in the Yuri-Honji district [10] and in women aged 14–34 years according to the National Health and Nutrition Examination Survey in the United States between 2003 and 2018 [11]. Additionally, even one vaccination dose has decreased persistent HPV16 and HPV18 infections in Indian women aged 10–18 years [12] and African women aged 15–20 years [13].

Despite the domestic introduction of the HPV vaccine and existing studies on its effects in various races, there have been limited studies on its efficacy in a cohort of Korean women infected with HPV. Seong et al. reported an adjusted prevalence ratio of 0.51 for HPV16 and HPV18 in vaccinated Korean women aged 20–60 years with positive atypical squamous cells of undetermined significance (ASCUS) and LSIL [14]. However, this study did not cover persistent HPV infection or VL. Therefore, our study aimed to fill this gap by examining the efficacy of the HPV vaccine against persistent HPV infection and VL in the Korea HPV cohort.

MATERIALS AND METHODS

1. Study design and participants

To investigate the risk factors associated with the progression to HSILs, Korean women who were tested positive on HPV DNA and diagnosed with ASCUS/LSIL on Papanicolaou (PAP) smear were recruited from 6 hospitals [15]. A total of 1,757 women aged 20–60 years were enrolled between 2010 and 2021 and underwent pathological examination, including PAP smear and HPV DNA tests every 6 months. Medical staff conducted interviews to collect

information on vaccination history, such as vaccination doses and duration, and sexual history, such as age of sexual debut, contraceptive status, and number of sexual partners. Each hospital obtained approval from its respective Institutional Review Board (IRB) to recruit participants. Furthermore, we obtained IRB approval from the Korea Disease Control and Prevention Agency to analyze participant information (No. 2018–06-02-P-A).

2. Study samples

We obtained 96 clinical DNA samples from the 1,757 study participants from the National Biobank of Korea (NBK), part of the Korea Centers for Disease Control and Prevention (KCDC), in accordance with the NBK guidelines. The sample set comprised 58 samples from 24 vaccinated and 34 unvaccinated HPV16-infected women, and 38 samples from 22 vaccinated and 16 unvaccinated HPV18-infected women. Approval for the use of these samples in our study was granted by the KCDC Research Ethics Committee (2019-01-06).

3. Determination of HPV load and PS

The HPV E6 gene was used to measure the total VL and HPV E2 gene to determine the PS. This is because E2 and E6 exist equally in the episomal state, whereas E2 is lost in the integration process [16]. To determine the HPV load and PS of 96 study samples, quantification of HPV E6 and E2, as well as globin genes, was performed using the Exicycler 96 Real-Time Quantitative Thermal Block and AccuPower Plus DualStar qPCR PreMix & Master Mix (Bioneer, Daejeon, Korea). PCR was performed under the following conditions: step 1, 95°C for 5 minutes; and step 2, (95°C for 5 seconds, 60°C for 30 seconds)×45 cycles/scan. The gene sequences are listed in **Table S1**. To quantify the copy numbers of HPV16, HPV18, and globin in 5-μl samples, standard curves were created with 5-fold serial dilutions of the WHO HPV16 and HPV18 international standards (NIBSC, London, UK) and globin DNA in the pBHA vector, respectively. The viral copy numbers were normalized to cellular DNA using the following formula: HPV Load (Copy/Cell)=Number of HPV Copies/(Number of Globin Copies/2) [17]. The PS of HPV DNA in the host genome was confirmed using the E2:E6 ratio and defined as follows: E2/E6=0 (fully integrated), E2/E6≥0.95 (episomal), and 0<E2/E6<0.95 (mixed form) [18].

4. Definition of persistence and clearance

Persistence is defined as the detection of the same genotype on 3 or more consecutive tests during the entire tracking period, whereas clearance refers to the absence of the genotype after a positive test result. Cases with uncertain clearance were excluded from the clearance group, as shown in **Table S2**.

5. Statistical analysis

The Cochran–Armitage trend tests were performed to analyze vaccination and prevalence trends over the 12-year study period. Descriptive statistics, including frequencies and percentages, were used to summarize categorical variables, and the chi-square tests were performed to evaluate differences in proportion between each categorical variable in the vaccinated and unvaccinated groups. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The mean±standard error of the mean (SEM) values were calculated using Prism 5 (GraphPad, San Diego, CA, USA) and compared using an unpaired t-test. Statistical significance was set at $p<0.05$.

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RESULTS

1. HPV16/18 prevalence at registration by HPV vaccination

Of 1,757 women enrolled in this study, 21 and 76 were sequentially excluded due to missing vaccination and genotype data, respectively (Fig. S1). The remaining 1,660 women with available baseline information were divided into vaccinated (n=512) and unvaccinated (n=1,148) groups; thus, the vaccination rate in this cohort was approximately 30%. The characteristics of the enrolled participants are summarized in **Tables S3** and **S4**. The number of registrants by year is shown in **Table 1** according to vaccination status and genotype at registration. Next, vaccination and prevalence rates of HPV16/18 by year were calculated. Over time, the vaccination rate increased from 14.3% to 60.7% (p-trend<0.001), and the prevalence of HPV16/18 in the vaccination group decreased from 18.5% to 11.8% (p-trend=0.025). However, there was no significant change trend in the prevalence rate of the unvaccinated group (p-trend=0.292). Statistical analysis was conducted, except for the years 2019 and 2021, when fewer than 10 registrants were registered. In addition, improved awareness of HPV vaccines reduced the average age of the vaccinated group by 7 years for approximately 10 years after the introduction of the National Immunization Program (NIP): from 34 years in 2010 to 27 years in 2020 (data not shown). The data presented in **Table 1** suggest that the increased uptake of HPV vaccination in Korea has decreased the prevalence rate of HPV16/18 among vaccinated individuals.

2. Prevalence of HPV16/18 during the follow-up by HPV vaccination status

Genotype data were collected at registration and during the follow-up period for 1,660 registrants tracked every 6 months (**Table 2**). The number of visits was divided into 1–12 times to determine whether the number of visits between the vaccinated and unvaccinated groups needed to be adjusted; no significant difference was found (**Table S5**). The total number of HPV types—regardless of co-infection status—was counted for 512 vaccinated and 1,148 unvaccinated women, resulting in 2,649 and 5,338 HPV types, respectively. Each percentage was calculated for HPV16/18 or other types, and the HPV16/18 prevalence of the vaccinated and unvaccinated groups showed a significant difference of 7.1% and 10.3% (p<0.001), respectively. Although this is not a typical analytic method to evaluate the effectiveness of a vaccine—particularly the prevalence rate—it provides meaningful data that can indirectly confirm the long-term effect of vaccination.

Table 1. HPV16/18 prevalence at registration by HPV vaccination

Variables	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
No. of registered women													
Vaccinated													
HPV16/18	5	11	11	8	8	1	4	8	5	0	6	1	68
Other types	22	43	56	46	29	30	31	64	42	1	45	5	414
Unvaccinated													
HPV16/18	23	53	30	23	23	9	13	13	11	0	6	1	205
Other types	139	166	196	111	80	46	73	81	52	0	27	2	973
Total	189	273	293	188	140	86	121	166	110	1	84	9	1,660
Rates (%)													p-trend
Vaccination rate	14.3	19.8	22.9	28.7	26.4	36.0	28.9	43.4	42.7	100.0	60.7	66.7	<0.001
HPV16/18 prevalence													
Vaccinated	18.5	20.4	16.4	14.8	21.6	3.2	11.4	11.1	10.6	0.0	11.8	16.7	0.025
Unvaccinated	14.2	24.2	13.3	17.2	22.3	16.4	15.1	13.8	17.5	0.0	18.2	33.3	0.292

The rates of vaccination and prevalence by year were analyzed using the Cochran–Armitage trend test. Statistical significance was set at p<0.05.
HPV, human papillomavirus.

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Table 2. Prevalence of HPV16/18 during the follow-up by HPV vaccination status

HPV types	Vaccinated	Unvaccinated	p-value
HPV16/18	187 (7.1)	551 (10.3)	<0.001
Other types	2,462 (92.9)	4,787 (89.7)	
Total	2,649 (100.0)	5,338 (100.0)	

Values are presented as number (%).
The difference in proportion between each categorical variable was evaluated using the chi-square test.
Statistical significance was set at $p<0.05$.
HPV, human papillomavirus.

Table 3. Mean viral load of HPV16 and HPV18 according to vaccination status

Variables	Vaccinated	Unvaccinated	p-value
Total viral load			
HPV16	0.437±0.162 (21)	2.477±0.776 (33)	0.048
HPV18	0.335±0.174 (19)	0.013±0.004 (11)	0.172
E2/E6 ratio			
HPV16	0.529±0.060	0.371±0.028	0.010
HPV18	1.466±0.333	0.279±0.110	0.011

Each mean±standard error of the mean was evaluated using an unpaired t-test, and statistical significance was set at $p<0.05$.
HPV, human papillomavirus.

3. Mean VL of HPV16 and HPV18 according to vaccination status

The HPV16 VL was notably higher in 33 unvaccinated samples than in 21 vaccinated samples (p=0.048); this trend was absent for HPV18 (p=0.172). Conversely, the E2:E6 ratio was significantly higher in 19 vaccinated samples than in 11 unvaccinated samples of HPV18 (p=0.011) and HPV16 (p=0.010). The mean±SEM value of each total VL and E2:E6 ratio are summarized in **Table 3**, and 12 "undetected" samples were excluded from the analysis.

4. PS of HPV16 and HPV18 according to vaccination status

The PS of HPV DNA in the host genome was confirmed using the E2:E6 ratio (**Table 4**). In the case of HPV16, the episomal rate of the vaccinated group (14.3%; 3/21) was higher than that of the unvaccinated group (0%; 0/33), and the integrated rate of the vaccinated group (0%; 0/21) was lower than that of the unvaccinated group (6.1%; 2/33). However, most viruses were present in a mixed form in both the vaccinated (85.7%; 18/21) and unvaccinated groups (93.9%; 31/33). By contrast, in HPV18, the integrated rate of the vaccinated and unvaccinated groups showed marked differences of 5.3% (1/19) and 54.5% (6/11), respectively. Taken together, vaccination reduces the total VL of HPV16 and increases the E2:E6 ratio by maintaining the PS in the episomal form for HPV16 and HPV18 (especially).

Table 4. Physical state of HPV16 and HPV18 according to vaccination status

Physical state	Vaccinated	Unvaccinated
HPV16		
Integrated	0 (0.0)	2 (6.1)
Mixed	18 (85.7)	31 (93.9)
Episomal	3 (14.3)	0 (0.0)
HPV18		
Integrated	1 (5.3)	6 (54.5)
Mixed	8 (42.1)	4 (36.4)
Episomal	10 (52.6)	1 (9.1)

Values are presented as number (%).
The physical state was determined in terms of integrated (E2:E6=0), mixed (0<E2:E6<0.95), and episomal form (E2:E6≥0.95).
HPV, human papillomavirus.

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5. Changes in the duration of HPV16 and HPV18 infections by HPV vaccination status

Following the first exclusion (**Fig. S1**), a subset of 512 vaccinated and 1,148 unvaccinated participants was further excluded owing to a lack of history and traceability of HPV16/18 infection, as shown in **Fig. S2**. Data from the remaining participants were used to investigate changes in infection duration by vaccination status. Ultimately, 37 and 19 traceable registrants among vaccinated women with HPV16 and HPV18 infection, respectively, and 87 and 45 traceable registrants among unvaccinated women with HPV16 and HPV18 infection, respectively, were included in the infection duration analysis.

Genotype data collected every 6 months were classified by infection duration (**Table 5**). Approximately half of all groups were clear from infection in less than 6 months. The vaccinated group had a higher clearance rate (56.8% and 68.4%) and a lower persistence rate (43.2% and 31.6%) than did the unvaccinated group for both HPV16 and HPV18. HPV vaccination tended to reduce infection duration except for n<6 months. HPV16 infection duration analysis showed that the vaccinated group had a greater proportion (10.8% and 21.6%) than did the unvaccinated group (9.2% and 13.8%) in 6≤n<18 months but a lower proportion (10.8%) in n≥18 months. For HPV18, the vaccinated group had a higher proportion (21.1%) than did the unvaccinated group (11.1%) in 6≤n<12 months but a lower proportion (15.8% and 5.3%) in 12≤n<24 months. In summary, HPV vaccination tends to shorten the duration of persistent infection.

6. HPV vaccine mechanism to reduce infection duration

Finally, we investigated the relationship between infection duration and VL based on the one-dimensional vaccine effects described above such as prevalence, VL, and persistence. Among the 84 samples shown in **Table 3**, the ones that conformed to the final inclusion definition (**Fig. S2**) were selected. When comparing the VLs of the persistence and clearance groups, the persistence VLs of the unvaccinated groups were 6 and 2 times greater in HPV16 and HPV18, respectively, suggesting a positive correlation between duration of infection and VL (**Table 6**). When comparing the VL according to vaccination status, the HPV16 VL in the vaccinated group was about 4 times smaller than that in the unvaccinated group, regardless of the infection duration. Moreover, the persistence rate of the vaccinated group (70.6%; 12/17) was lower than that of the unvaccinated group (90.0%; 27/30) with regards to HPV16. By contrast, HPV18 VL in the vaccinated group was about 3.5 times lower than that in the unvaccinated group in the clearance, but not the persistence, group. Although we could not achieve statistical significance owing to the small sample size, vaccination showed a tendency to reduce the HPV16 VL proportional to the duration of infection.

Table 5. Changes in the duration of HPV16 and HPV18 infections by HPV vaccination status

Duration of infection	HPV16		HPV18	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Clearance*	21 (56.8)	48 (55.2)	13 (68.4)	28 (62.2)
<6	17 (45.9)	40 (46.0)	9 (47.4)	23 (51.1)
≥6 and <12	4 (10.8)	8 (9.2)	4 (21.1)	5 (11.1)
Persistence†	16 (43.2)	39 (44.8)	6 (31.6)	17 (37.8)
≥12 and <18	8 (21.6)	12 (13.8)	3 (15.8)	11 (24.4)
≥18 and <24	4 (10.8)	11 (12.6)	1 (5.3)	5 (11.1)
≥24	4 (10.8)	16 (18.4)	2 (10.5)	1 (2.2)
Total	37 (100.0)	87 (100.0)	19 (100.0)	45 (100.0)

Values are presented as number (%).
HPV, human papillomavirus.
*The other cases except for persistent infections; †Identification of identical genotype more than 3 consecutive times over the entire tracking period using the HPV DNA test conducted every 6 months.

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Table 6. HPV vaccine mechanism to reduce infection duration

Variables	Vaccinated	Unvaccinated
HPV16		
Persistence	0.622±0.240 (12)	2.518±0.862 (27)
Clearance	0.112±0.104 (5)	0.432±0.300 (3)
HPV18		
Persistence	0.567±0.285 (11)	0.015±0.006 (8)
Clearance	0.002±0.002 (2)	0.007±0.003 (2)

Mean±standard error of the mean values were calculated using Prism 5 (GraphPad, San Diego, CA, USA).
HPV, human papillomavirus.

DISCUSSION

To the best of our knowledge, this study is the first to investigate changes in HPV16 and HPV18 prevalence over a 12-year period following vaccination in Korean women with HPV infection. Our findings suggest that vaccination can regulate the duration of infection and reduce the risk of disease progression by lowering the VL.

Persistent HPV infection is known to increase the risk of cervical disease progression [19]. In this study, progression rates to HSIL were calculated based on the duration of infection (data not shown). The persistence group included progression within the infection period, whereas the clearance group included progression within 2 years after clearance. In HPV16, the progression rates of vaccinated and unvaccinated groups were higher in the persistence group (43.8%, 7/16 and 33.3%, 13/39, respectively) than in the clearance group (9.5%, 2/21 and 20.8%, 10/48, respectively). For HPV18, the progression rates of vaccinated and unvaccinated groups were also higher in the persistence group (16.7%, 1/6 and 23.5%, 4/17, respectively) than in the clearance group (7.7%, 1/13 and 14.3%, 4/28, respectively). Therefore, HPV vaccination is important for shortening infection duration (**Table 5**) and regulating progression in cases of long-lasting infection.

There are 2 limitations to this study. The first limitation is insufficient samples. For persistence analysis, only 11.9% (61/512) and 6.4% (33/512) of vaccinated women and 16.9% (194/1148) and 8.4% (96/1148) of unvaccinated women were infected with HPV16 and HPV18 at least once, respectively (**Fig. S2**). Additionally, non-traceable samples were again excluded from the study due to the strict definition of infection duration. As a result, only 37 and 19 women who received the vaccine and 87 and 45 women who were unvaccinated were included in the final groups for HPV16 and HPV18, respectively (**Table 5**). Furthermore, for the VL analysis presented in **Table 6**, obtaining enough samples for analysis was challenging because of the added classification of persistence and clearance along with the strict definition of infection duration. The second limitation is the characteristic differences between the vaccinated and unvaccinated groups (**Table S3**). The distribution of all categories, including age, sexual debut age, number of sexual partners (last 1 year), and contraception, was related to vaccination. The average age of sexual debut was similar between the vaccinated and unvaccinated groups at 22.2±4.0 and 23.4±5.6 years, respectively. However, there was a considerable difference in biological age, with the vaccinated group having a mean age of 33.0±7.1 and the unvaccinated group of 42.3±9.9 years. There was also a slight difference between the groups in the percentage of women who reported using contraception, with 57.6% in the vaccinated group and 45.4% in the unvaccinated group. Despite these limitations, it is interesting to note that 60% of women in the study received their first vaccine dose after the recommended vaccination age (**Table S4**). The vaccine still significantly reduced prevalence, persistence, and VL in these women.

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Marongiu et al. [20] observed that the median HPV16 VL was higher than that for HPV18 in low grade (LG, 6.59 and 1.35 copy number/cell [c/c]) and high grade (HG, 6.87 and 0.20 c/c) when the normal VL was low and similar (0.04 and 0.03 c/c). By contrast, the fully integrated rate in HPV16 is lower than that for HPV18 in LG (6.25 and 12.5%) and HG (9.1 and 20%, respectively). Moreover, HPV loads that appeared higher than normal in LG and HG were proposed as a potential biomarker for cervical disease; however, an integrated state that showed no difference between normal, LG, and HG was not suggested. Yoshida et al. [21] said that the mean c/c was higher for HPV16 and much lower for HPV18 (4.27 and 1.20, p=0.020). Moreover, when the mean c/c is significantly lower in the pure integrated case than in the nonintegrated case due to the absence of E2 (0.43 and 6.13, p=0.020), the mean c/c of HPV18 was lower than that of HPV16 in the pure integrated case (0.28 and 1.51, p=0.001). They suggested that many HPV18 were in a pure integrated state because of its low c/c. Segondy et al. [22] showed that not only the median VL (log E6 DNA copies/1,000 cells) was higher in HPV16 cases than in HPV18 cases with CIN, but also a high baseline HPV16 VL was strongly related to persistence lasting 16 months at CIN2 and above, but not for HPV18. Similar to the study described earlier, Trevisan et al. [23] and Muñoz et al. [24] found that the duration of infection is proportional to the VL in the Ludwig–McGill Cohort Study and a cohort of Colombian women, respectively. Lastly, van der Weele et al. [25] reported that VL and incidence of HPV16 were reduced by inoculating the bivalent HPV vaccine in both clearing and persistent infections, explaining the possibility that the T cell-mediated immune responses would limit viral replication. These findings are consistent with our results that HPV16 has a higher VL than HPV18 and that HPV18 exists in an integrated state more often than HPV16. In addition, the VL is a biomarker for cervical disease with a higher HPV16 VL associated with persistence, and the HPV vaccine reduces the VL and incidence of HPV16 infection. These findings also support our results that HPV vaccination shortens the duration of infection by controlling the VL and mitigate our limitation of a small sample size for analysis.

Despite the implementation of aggressive policies to prevent cervical cancer in Korea, including cervical cancer screening and the NIP for HPV vaccination, cervical cancer remains a significant threat to Korean women. Our HPV cohort study—the longest since MFDS approval of the HPV vaccines in 2007 and 2008—highlights the gap in the perception of vaccination by age, with a 9-year age difference between vaccinated and unvaccinated groups (**Table S3**). Furthermore, our study revealed that 60% of all vaccinated women exceeded the recommended vaccination age (**Table S4**). However, the age of vaccination gradually decreases every year, and the vaccination effects appear even in 60% of women who not only exceed the recommended vaccination age but are also vaccinated after their first sexual intercourse (average age 22 years). The women who were part of the NIP introduced in June 2016 for women aged 12–17 are now adults aged 19–24 years. Our data—predating the introduction of NIP—can be used as a valuable comparator for these adult women and future NIP participants. In addition, based on this study, which observed the effectiveness of the HPV vaccine in terms of prevalence, persistence, and progression of HPV infection in women over the age of 26 years, we propose to expand the age of NIP in low-income women between the ages of 18 and 26 to further reduce the burden of cervical cancer in Korea.

The latest paper includes the following. Despite the effectiveness of HPV vaccines that can prevent 70%– 90% of HPV-attributable cancers, there are countries where vaccination rates are declining [26]. In Korea, through the HPV cohort study, it was confirmed that the inoculation rate increased and the inoculation age decreased every year (**Table 1**). In an effort to improve the awareness of HPV, public service advertisements and school education are

being implemented, and NIP was expanded from 12-year-olds to female adolescents aged 12 to 17 and low-income women aged 18 to 26 [27]. In addition, to reduce morbidity and mortality from cervical cancer, a national cervical screening program is as important as NIP. Korean women over the age of 20 undergo free cervical cytology screening every 2 years [28], but in countries where regular screening is difficult nationwide due to a lack of laboratories and pathologists, using 'careHPV', self-sampled HPV testing, may be a good alternative [29]. Another paper suggested performing HPV classification for ASCUS cases and retesting HPV-negative cases after 2 years, because the cumulative risk ratio of CIN3+ over 2 years was sufficiently low at 0.3 for ASCUS/HPV-compared to NILM cases [30]. These results can help in national policy decisions on HPV, such as selecting essential groups for support projects and determining detailed care guidelines. Lastly, there is a growing interest in the development of therapeutic vaccines that can be used for women suffering from advanced HPV-related diseases, including cervical cancer, or who have not received prophylactic HPV vaccination [31,32]. There is no approved HPV vaccine for treatment so far, but various platforms based on peptide, protein, DNA, RNA, bacterial, and viral vector vaccines are being studied for the development of therapeutic vaccines [33]. Development of therapeutic vaccines is vital to the global strategy of the World Health Organization, which could save more than 62 million lives by 2120.

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SUPPLEMENTARY MATERIALS

Table S1
Primers and probes used for quantitative polymerase chain reaction

Table S2
Clearance definition

Table S3
Clinical characteristics of the study participants

Table S4
Clinical characteristics of the study participants

Table S5
Number of HPV genotyping tests per participant, 2010–2021

Fig. S1
Flowchart of participant inclusion and exclusion process.

Fig. S2
Flowchart of participant inclusion and exclusion for persistence analysis.

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