



# Long-term follow-up of human papillomavirus type replacement among young pregnant Finnish females before and after a community-randomised HPV vaccination trial with moderate coverage

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## Abstract

Large scale human papillomavirus (HPV) vaccination against the most oncogenic high-risk human papillomavirus (HPV) types 16/18 is rapidly reducing their incidence. However, attempts at assessing if this leads to an increase of nonvaccine targeted HPV types have been hampered by several limitations, such as the inability to differentiate secular trends. We performed a population-based serological survey of unvaccinated young women over 12 years. The women were under 23-years-old, residents from 33 communities which participated in a community-randomised trial (CRT) with approximately 50% vaccination coverage. Serum samples were retrieved pre-CRT and post-CRT implementation. Seropositivity to 17 HPV types was assessed. HPV seroprevalence ratios (PR) comparing the postvaccination to prevaccination era were estimated by trial arm. This was also assessed among the sexual risk-taking core group, where type replacement may occur more rapidly. In total, 8022 serum samples from the population-based Finnish Maternity Cohort were retrieved. HPV types 16/18 showed decreased seroprevalence among the unvaccinated in communities only after gender-neutral vaccination ( $PR_{16/18A} = 0.8$ , 95% CI 0.7-0.9). HPV6/11 and

**Abbreviations:** CI, confidence intervals; CRT, community-randomised trial; FMC, Finnish Maternity Cohort; GEE, generalised estimating equation; HBV, hepatitis B vaccine; HPV, human papillomavirus; HSV-2, herpes simplex virus type II; IARC, International Agency for Research on Cancer; ICC, intracluster correlation coefficient; P, seroprevalence; PR, seroprevalence ratio; RPR, ratio of seroprevalence ratios.

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HPV73 were decreased after gender-neutral vaccination ( $PR_{6/11A} = 0.8$ , 95% CI 0.7-0.9,  $PR_{73A} = 0.7$ , 95% CI 0.6-0.9, respectively) and girls-only vaccination ( $PR_{6/11B} = 0.8$ , 95% CI 0.7-0.9,  $PR_{73B} = 0.9$ , 95% CI 0.8-1.0). HPV68 alone was increased but only after girls-only vaccination ( $PR_{68B} = 1.3$ , 95% CI 1.0-1.7,  $PR_{core68B} = 2.8$ , 95% CI 1.2-6.3). A large-scale, long-term follow-up found no type replacement in the communities with the strongest reduction of vaccine HPV types. Limited evidence for an increase in HPV68 was restricted to girls-only vaccinated communities and may have been due to secular trends (ClinicalTrials.gov number: NCT00534638).

#### KEYWORDS

community-randomised trial, core-group, HPV, serosurvey, type replacement

## 1 | INTRODUCTION

Oncogenic human papillomavirus (HPV), the necessary cause of cervical cancer,<sup>1</sup> is a well-established causal agent of several anogenital and oropharyngeal cancers. There are currently three efficacious HPV-vaccines licensed which target the two most high-risk HPV types HPV16 and 18, (the two first-generation vaccines, Cervarix and Gardasil), or five additional high-risk HPV types, HPV31, 33, 45, 52 and 58 (the nonavalent vaccine, Gardasil9).<sup>2</sup> Since 2007, these vaccines have been gradually implemented in national vaccination programs.<sup>3</sup> However, there are a total of 12 high-risk HPV types which are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans, HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, with a further eight types classified as possibly (or probably) carcinogenic, HPV26, 53, 66, 68, 67, 70, 73 and 83.<sup>4</sup> As such, concern has been flagged over a decade ago, whether such selective vaccination could induce HPV type replacement to occur.<sup>5</sup> By removing selected HPV types, vaccination may disrupt the dynamic equilibrium among HPV types. Subsequently, the vacant niche may become superceded by one or more of the nonvaccine types. This vaccine-induced evolutionary response in the niche habitation by the nonvaccine types has already been described in analogous situations, for example, following vaccination against *Streptococcus pneumoniae*, and is commonly known as type replacement.<sup>6,7</sup>

Several studies have evaluated the occurrence of HPV type replacement, using differing methodologies; comparison of the HPV prevalence between the postvaccination and prevaccination era,<sup>8-10</sup> between vaccinated and unvaccinated persons in the postvaccination era<sup>11</sup> or via individually randomised HPV vaccination trials.<sup>12</sup> Importantly, a recent meta-analysis of the above-mentioned studies found an increasing trend in the pooled nonvaccine targeted (and noncross-protected) HPV types,<sup>13</sup> further to an earlier meta-analysis which found possible increases in HPV 39 and 52.<sup>14</sup>

However, there are multiple major limitations when evaluating the occurrence of HPV type replacement. When conducting post-vaccination era surveillance and comparing the HPV prevalence prevaccination and postvaccination era, it is difficult to distinguish possible increases due to vaccine induced-type replacement from that

### What's new?

Vaccination efforts have decreased the prevalence of oncogenic HPV types, such as HPV 16/18. This may create space for other types to expand, but it is difficult to distinguish the effect of the vaccine from long-term temporal trends. Here, the authors conducted a community-randomized trial in 33 communities. Each group of 11 communities received either gender-neutral HPV vaccination, girls-only HPV vaccination, or gender neutral hepatitis vaccination. In the girls-only arm, vaccination reduced the prevalence of HPV 6/11, and HPV 68 increased in prevalence. However, this effect may have been due to secular trends.

due to secular trends. On the other hand, evaluating type replacement by means of negative vaccine effectiveness in the postvaccination era, may be an unsuitable measure for both the identification and prediction of type replacement occurrence. That is, type replacement may be subdued in the vaccinated by vaccine-induced cross-protection, while manifesting with lesser limitation in the unvaccinated due to the indirect impacts of community-wise vaccination.<sup>15</sup> Last but not least, when evaluating type replacement via individually randomised clinical trials, it is likely that any estimates will underestimate the probability of type replacement, as the vaccination-induced selective pressure stems from too small a proportion of the population in comparison to that present after community-wise vaccination.<sup>16</sup>

Further to these, following vaccination against several other pathogen types, there has been a transitory "honeymoon period" immediately following vaccination implementation, before arriving at a new endemic equilibrium.<sup>17,18</sup> In the context of HPV vaccination, a recently published modelling study has found that there may be a HPV type replacement "honeymoon period" following vaccination, wherein nonvaccine types may at first appear to remain stable or even decrease before rebounding due to type replacement after a certain

incubation period since vaccination initiation.<sup>15</sup> Thus, previous inconclusive findings of any HPV type replacement may have been premature to identify type replacement occurrence.

We now evaluate the occurrence of HPV type replacement in a decade following a large population-based community-randomised HPV vaccination trial with close to 50% vaccination coverage (beginning in October 2007), by conducting a survey of HPV seroprevalence in unvaccinated Finnish female community residents over the pretrial and posttrial era. Herpes simplex virus type II (HSV-2) serology is an established marker of sexual risk taking, thereby we now utilise this as a proxy of core group membership,<sup>19</sup> to further investigate the occurrence of type replacement also within the core-group (the assortative subgroup of the population with high sexual contact rates), as it has been suggested that HPV type replacement may first manifest within this group.<sup>20</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and materials

The material of our study comprises of longitudinal population-based biobank follow-up of the Finnish community-randomised HPV vaccination trial evaluating the comparative effectiveness of girls-only or gender-neutral HPV vaccination (NCT00534638).<sup>21-23</sup>

Briefly, in 2007, 33 Finnish communities were stratified according to preascertained HPV16/18 seroprevalence,<sup>24</sup> into those with low, moderate or high seroprevalence. From each seroprevalence strata, the communities were then randomised to one of three trial arms, with an allocation ratio of 11:11:11.<sup>21</sup> All Swedish or Finnish speaking 1992 to 1995 born adolescents who were residing in the trial communities were identified via the Finnish Population Register and were invited in 2007 to 2010 to participate in the trial.<sup>21</sup> Of the 80 272 invited, a total of 20 513 females and 11 662 males participated in the trial from 2007 to 2010, with informed parental, guardian or participant consent (if aged 15 years old). In Arm A, a gender-neutral HPV vaccination strategy was applied to the communities, in Arm B a girls-only HPV vaccination strategy was applied and in Arm C a gender-neutral vaccination strategy was applied using the Hepatitis B (HBV) vaccine, thereby serving as the control Arm.<sup>21,23</sup> No organised HPV vaccination was administered to the birth cohorts following the trial birth cohorts until November 2013, when the Finnish national HPV vaccination program was initiated targeting those born in 1998 and younger.

The indirect effects of the trial were followed up by a population-based serological survey of unvaccinated women under the age of 23-years-old from 2005 until 2016, representing both the periods pre-HPV and post-HPV vaccination.<sup>22</sup> This was achieved by retrieving all the available first pregnancy serum samples from the Finnish Maternity Cohort (FMC), from women under 23-years-old at the time of donation within the sampling time frame, who had been resident in one of the 33 trial communities at the time of sample donation. The Finnish Maternity Cohort is a population-representative biobank

housing approximately 2 million samples (the Finnish population is approximately 5.5 million), established in 1983. Since 1983, all pregnant women in Finland have been invited to donate the residual volume of their blood sample after the mandatory testing for congenital infections for future research purposes; approximately 96% consent.<sup>25</sup> The vaccination status of the women was confirmed via linkage of the eligible FMC subjects with the HPV vaccination trial registry for all women, and via manual scrutinization of the subject's antibody titres for those women from the birth cohorts previously eligible for HPV vaccination via the Finnish National vaccination program (those born from 1998 and younger).

Among the 1992, 1993, 1994 and 1995, birth cohorts initially receiving HPV vaccination in the trial arms, community-wise vaccination coverage among females was 44.0%, 45.5%, 51.9% and 48.2% in the gender-neutral vaccination arm, 45.2%, 44.2%, 46.5% and 45.4% in girls-only vaccination arm and 0% in all four birth cohorts among the control arm (Figure 1). Among the same birth cohorts, the community-wise vaccination coverage among the males was 18.3%, 16.9%, 21.1% and 22.2% in the gender-neutral-vaccination Arm, whereas it was 0% among all four birth cohorts in girls-only vaccination and control arms. Among 1998, 1999 and 2000 birth cohorts receiving girls-only vaccination via the Finnish national vaccination program the vaccination coverage among females was 65.1%, 66.8% and 69.0%, respectively, in the communities which were also subject to the community-randomised trial.<sup>26</sup>

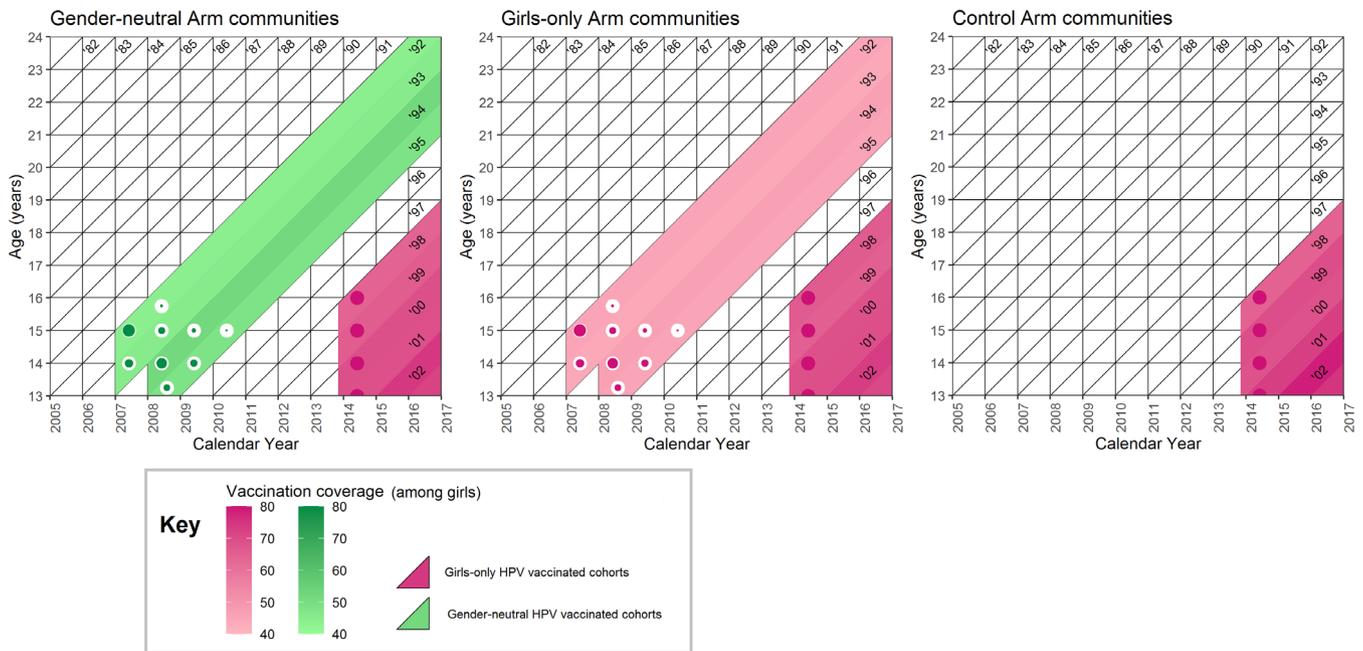
Information on self-reported maternal smoking among the pregnant females under the age of 23 from the same communities and sampling years 2005 to 2016 was garnered from the Finnish Medical Birth Registry.<sup>27</sup> Birth cohort-specific vaccination coverages for males and females by community and calendar year were gathered from the Finnish vaccination register.<sup>22,26</sup>

### 2.2 | Laboratory analyses

The retrieved FMC serum samples were analysed for the presence of serum antibodies to HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73 and herpes simplex virus type II (HSV-2) using heparin bound HPV pseudovirion and HSV-2 glycoprotein G 2 Luminex assay.<sup>22,28,29</sup> A negative control panel of serum samples from children under the age of 12-years-old was used to calculate HPV type-specific seropositivity cut-off values, by computing the median fluorescence intensities of the negative control serum panel plus three SDs.<sup>22</sup> For this study, the assay panel was extended to include also HPV51, 66 and HSV-2, more details of which are described in the Supporting Information Methods and reference 22.

### 2.3 | Statistical analyses

The magnitude of within-arm clustering was measured by calculating the intracluster correlation coefficient (ICC) using observations from 2005 to 2010, among all subjects and subjects stratified by HSV-2 seropositivity. The ICC of vaccine targeted and nonvaccine targeted



**FIGURE 1** Lexis diagrams describing the birth cohorts included in the study population. Each diagonal line represents an individual birth cohort, and the coloured fill the vaccination coverage among each birth cohort. The circles represent the years in which the particular cohorts received vaccination, and the coloured fill, the proportion of the total vaccination received that year [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

HPV was estimated using Fleiss and Cuzick's estimator and the accompanying 95% confidence intervals estimated using Zou and Donners modified Wald test.<sup>30,31</sup>

To evaluate the occurrence of HPV type replacement, the absolute seroprevalence of nonvaccine protected HPV39, 51, 56, 58, 59, 66, 68 and 73 was calculated among subjects stratified by trial Arm, and vaccination era (from 2005 to 2010 or 2011 to 2016, respectively the prevaccination or postvaccination era). Nonvaccine protected HPV types are defined as HPV types excluding bivalent vaccine targeted HPV16 and 18, and documented cross-protected types 31, 33, 35, 45 and 52. Within-arm HPV type-specific seroprevalence ratios, PR, were then estimated using a log binomial generalised estimating equation (GEE) model with an exchangeable correlation structure, comparing the postvaccination era seroprevalence, 2005 to 2010, to that in the prevaccination era, 2011 to 2016. All estimates were adjusted for era-specific community-wise maternal smoking as a proxy measure of general risk-taking behaviour. To evaluate the occurrence of type replacement among the core group, with-in arm PRs were similarly estimated among subjects who were HSV-2 seropositive (as a proxy measure of core-group membership). To take account for a possible delay between niche clearance and type replacement occurrence, with-in arm PRs were further stratified by the postvaccination era numerator, into the first or second postvaccination era, 2011 to 2013 or 2014 to 2016, respectively, compared to the entire prevaccination era. To assess whether observed increased with-in arm PRs were due to secular trends or type replacement, type specific with-in arm PRs from the intervention arms were compared to the with-in arm PRs from the control arm using the methodology of Altman and Bland.<sup>32</sup>

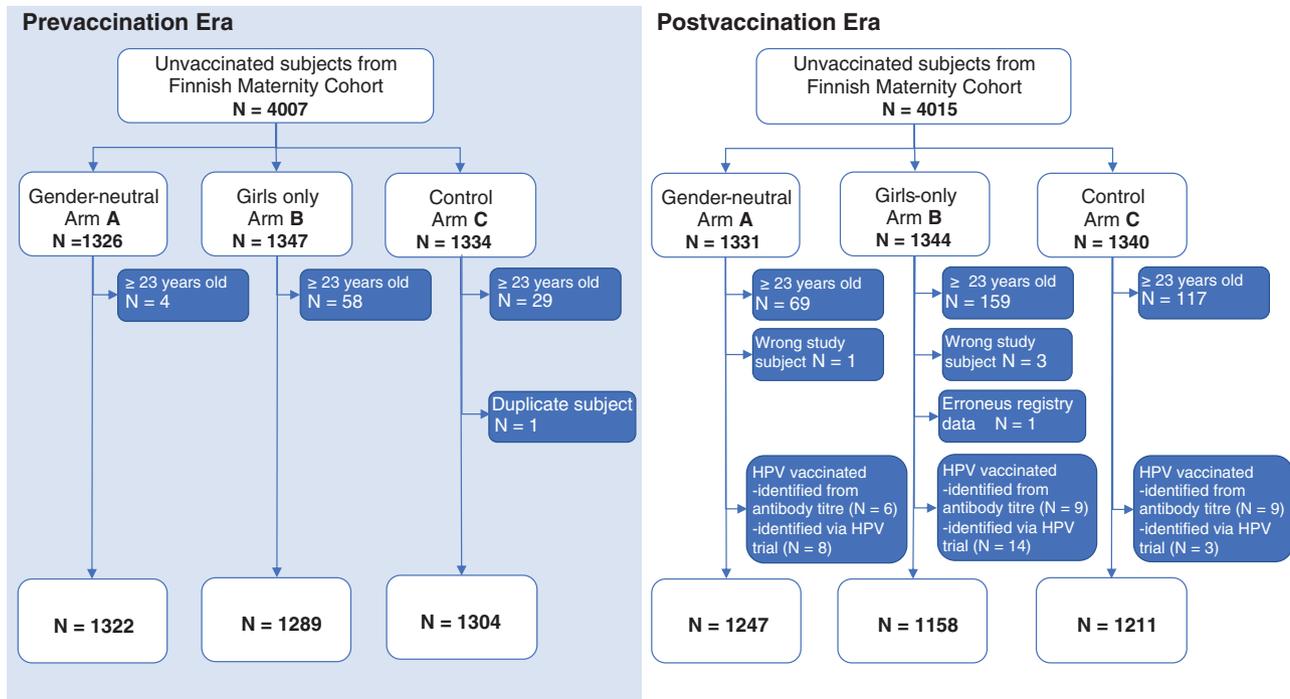
As a sensitivity analysis, probabilistic bias analysis was used to take account of misclassification owing to the known lack of seroconversion in a proportion of individuals following HPV infection. Previously<sup>33</sup> and currently ascertained (see Appendix for HPV51 and 66) specificity and sensitivity values of this heparin-bound HPV pseudovirion serology to identify cumulative infections were used. As a further sensitivity analysis, the HPV type-specific PRs were additionally estimated stratified by subjects age at the time of sample donation (into those aged 14- to 19-years-old and 20- to 22-years-old).

The statistical analyses were conducted using R software package (version 3.6.0.) with the following packages: ICCbin (version 1.1.1), geePack (version 1.2-1), episensr (version 0.9.5) for the analyses and ggplot2 (version 3.2.1) and LexisPlotR (version 0.3.2) for the graphical presentation of the results.

### 3 | RESULTS

#### 3.1 | Characteristics of the study

A total of 8022 unvaccinated pregnant subjects from the 33 trial communities were identified who had consented to participate in the Finnish Maternity Cohort during the years 2005 to 2016 while under the age of 23-years-old. Four thousand and seven were identified from the prevaccination years, 2005 to 2010, and 4015 from the postvaccination years, 2011 to 2016. From these subjects, 91 were excluded from the prevaccination years, and 345 from the postvaccination era, due to being over-aged when attending serum

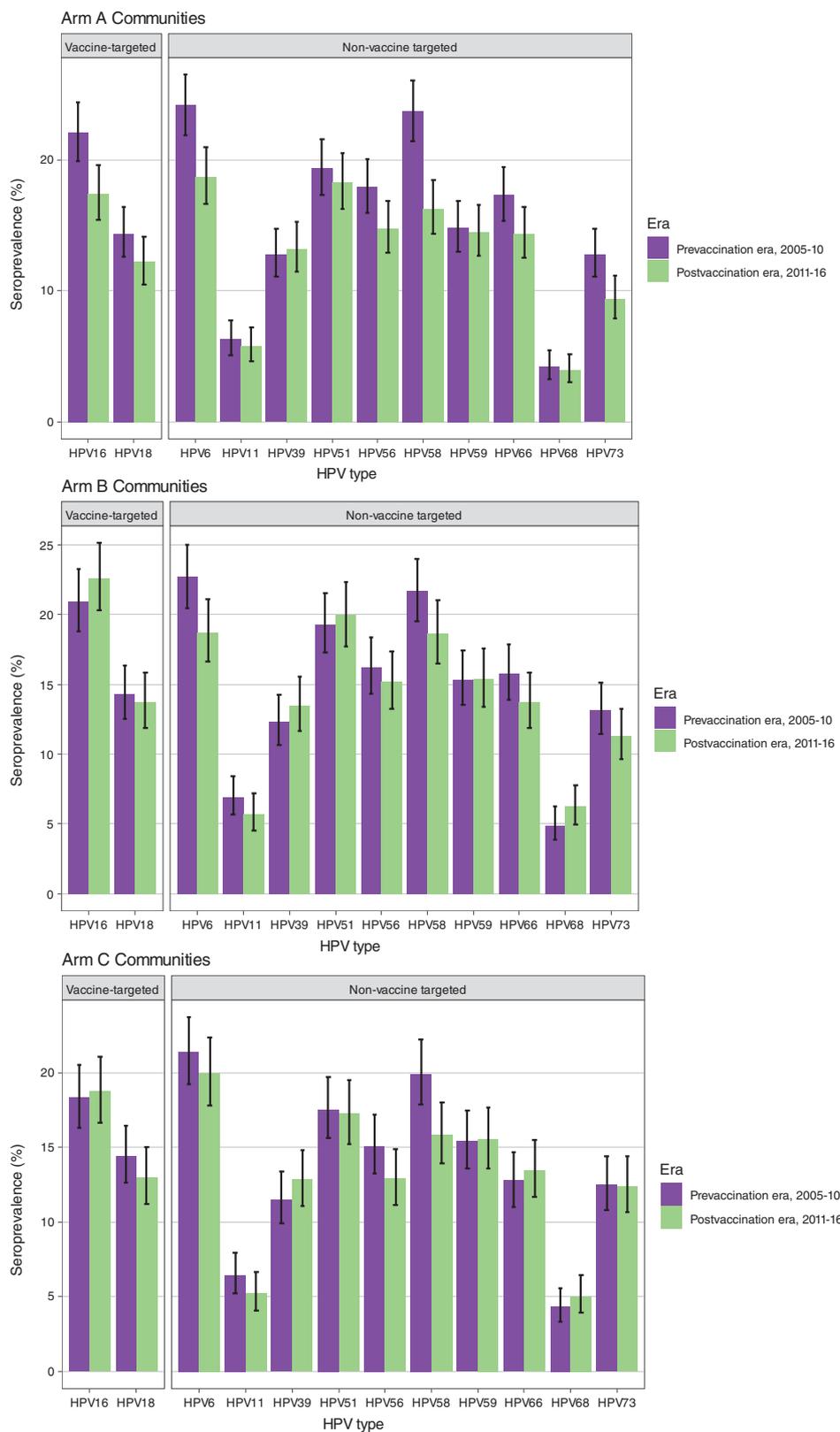


**FIGURE 2** Flow chart of the study population and all exclusions stratified by time period [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Characteristics of the prevaccination era and postvaccination era unvaccinated females according to trial Arm (gender-neutral vaccination Arm A, girls-only vaccination Arm B or control Arm C)

	Prevaccination Era (2005-2010)			Postvaccination Era (2011-2016)		
	Arm A (n = 1322) n (%)	Arm B (n = 1289) n (%)	Arm C (n = 1304) n (%)	Arm A (n = 1247) n (%)	Arm B (n = 1158) n (%)	Arm C (n = 1211) n (%)
<b>Birth cohort</b>						
1982-1983	126 (9.5)	115 (8.9)	111 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)
1984-1985	296 (22.4)	317 (24.6)	327 (25.1)	0 (0.0)	0 (0.0)	0 (0.0)
1986-1987	411 (31.1)	374 (29.0)	387 (29.7)	0 (0.0)	0 (0.0)	0 (0.0)
1988-1989	319 (24.1)	311 (24.1)	288 (22.1)	116 (9.3)	116 (10.0)	115 (9.5)
1990-1991	142 (10.7)	146 (11.3)	168 (12.9)	315 (25.3)	302 (26.1)	311 (25.7)
1992-1993	28 (2.1) <sup>a</sup>	26 (2.0) <sup>a</sup>	23 (1.8) <sup>a</sup>	424 (34.0)	409 (35.3)	415 (34.3)
1994-1995				272 (21.8)	231 (19.9)	250 (20.6)
1996-1997	0 (0.0)	0 (0.0)	0 (0.0)	105 (8.4)	89 (7.7)	106 (8.8)
1998-2000	0 (0.0)	0 (0.0)	0 (0.0)	15 (1.2)	11 (0.9)	14 (1.2)
<b>Age (years)</b>						
14-16	28 (2.1)	21 (1.6)	27 (2.1)	19 (1.5)	15 (1.3)	26 (2.1)
17-19	392 (29.7)	390 (30.3)	376 (28.8)	354 (28.4)	305 (26.3)	339 (28.0)
20-22	902 (68.2)	878 (68.1)	901 (69.1)	874 (70.1)	838 (72.4)	846 (69.9)
<b>Herpes simplex virus type 2 (HSV-2)</b>						
Positive	224 (16.9)	247 (19.2)	224 (17.2)	189 (15.2)	162 (14.0)	192 (15.9)
Negative	1098 (83.1)	1042 (80.8)	1080 (82.8)	1058 (84.8)	996 (86.0)	1019 (84.1)
<b>Arithmetic mean (SD)</b>						
Community-wise self-reported maternal smoking	38.4 (6.0)	36.7 (6.0)	42.8 (7.6)	37.8 (5.3)	38.6 (6.4)	43.3 (9.3)

<sup>a</sup>In the prevaccination era reporting for the 1992-1995 birth cohorts is merged to avoid reporting identifiable data due to small count numbers (n < 5).



**FIGURE 3** HPV type-specific seroprevalence (%) by trial Arm and vaccination era (prevaccination and postvaccination era, 2005-2010 and 2011-2016, respectively). The error bars signify the 95% confidence intervals [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

sampling. A total of 49 subjects from the postvaccination years were excluded due to being HPV vaccinated (as identified via registry linkage,  $n = 25$ , and via characteristically high antibody titres,  $n = 24$ ; Figure 2). From the initial subjects identified, a total of 3915 were included in the study from the prevaccination era and 3616 from the

postvaccination era. The intracluster correlation coefficient, ICC, among the postvaccination era approximated zero for high risk (hr) HPV16/18 (ICC = 0.007, 95% confidence intervals, CI 0.00-0.06), HPV39/51/56/58/59/66/68/73 (ICC = 0.009, 0.00-0.06) and low risk (lr) HPV6/11 (ICC = 0.001, 0.00-0.03).

**TABLE 2** Seroprevalence ratios (95% confidence intervals) comparing the seroprevalence in the postvaccination era, 2011-2016, to that in the prevaccination era among, A, all subjects and B, among the core-group (identified by herpes simplex virus type 2 seropositivity)

			Seroprevalence ratios (95% CI)		
			Unvaccinated Finnish females aged under 23 years		
			Postvaccination vs prevaccination era		
A	HPV type		Arm A (n = 1247 vs 1322)	Arm B (n = 1158 vs 1289)	Arm C (n = 1211 vs 1304)
Vaccine targeted	hr	16	0.79 (0.72-0.87)	1.09 (0.91-1.32)	1.01 (0.86-1.20)
		18	0.86 (0.70-1.06)	0.96 (0.74-1.24)	0.89 (0.70-1.13)
Nonvaccine targeted	lr	6	0.78 (0.67-0.92)	0.82 (0.75-0.91)	0.93 (0.82-1.05)
		11	0.93 (0.68-1.28)	0.78 (0.60-1.01)	0.80 (0.58-1.10)
		39	1.04 (0.88-1.22)	1.07 (0.85-1.33)	1.09 (0.92-1.31)
	hr	51	0.95 (0.78-1.17)	1.03 (0.91-1.15)	0.98 (0.80-1.20)
		56	0.83 (0.73-0.93)	0.93 (0.77-1.13)	0.85 (0.70-1.02)
		58	0.70 (0.63-0.79)	0.86 (0.72-1.03)	0.79 (0.65-0.96)
		59	0.99 (0.80-1.22)	1.00 (0.82-1.22)	1.00 (0.79-1.26)
		66	0.83 (0.73-0.96)	0.89 (0.73-1.08)	1.05 (0.89-1.24)
		68	0.94 (0.72-1.23)	1.28 (0.97-1.68)	1.16 (0.90-1.51)
	73	0.74 (0.60-0.91)	0.87 (0.76-1.00)	0.99 (0.85-1.15)	
			Seroprevalence ratios (95% CI)		
			Unvaccinated Finnish females aged under 23		
			Postvaccination vs prevaccination vaccination era		
B	HPV type		Arm A (n = 189 vs 224) HSV-2 positive	Arm B (n = 162 vs 247) HSV-2 positive	Arm C (n = 192 vs 224) HSV-2 positive
Vaccine targeted	hr	16	0.64 (0.50-0.81)	0.94 (0.63-1.42)	0.98 (0.70-1.38)
		18	0.95 (0.60-1.51)	0.74 (0.34-1.65)	1.00 (0.68-1.46)
Nonvaccine targeted	lr	6	0.61 (0.43-0.87)	0.43 (0.34-0.54)	0.95 (0.64-1.43)
		11	0.82 (0.48-1.39)	0.54 (0.21-1.37)	0.96 (0.51-1.81)
		39	0.77 (0.62-0.96)	0.90 (0.50-1.60)	1.10 (0.70-1.75)
	hr	51	0.71 (0.48-1.05)	1.04 (0.78-1.38)	1.14 (0.81-1.59)
		56	0.72 (0.55-0.94)	0.68 (0.43-1.07)	0.65 (0.40-1.05)
		58	0.65 (0.44-0.96)	0.79 (0.54-1.14)	0.64 (0.39-1.06)
		59	0.90 (0.75-1.09)	0.76 (0.54-1.07)	0.82 (0.57-1.18)
		66	0.72 (0.53-0.98)	0.76 (0.44-1.30)	0.79 (0.59-1.06)
		68	0.57 (0.23-1.38)	2.78 (1.23-6.31)	1.40 (0.79-2.49)
	73	0.45 (0.35-0.59)	0.84 (0.57-1.24)	0.86 (0.53-1.39)	

Note: Estimates are HPV type-specific including both low and high-risk nonvaccine targeted HPV types and to ensure niche clearance also vaccine targeted HPV16/18. Estimates are stratified by trial arm (hr, high risk HPV type; lr, low risk HPV type).

The demographics of the study subjects were comparable between the prevaccination and postvaccination eras. In both eras, the age distribution was left-skewed with the majority of subjects being aged 17 to 22 years old, and only a small minority being aged under 17 (Table 1). The shape of the birth cohort distribution remained the same in the prevaccination to postvaccination era, but with a shift towards the younger cohorts in the postvaccination era (from those born 1992 and younger, to those born in 1988 and younger; Table 1). The HSV-2 seroprevalence was somewhat reduced between the prevaccination and postvaccination eras among subjects from Arm B (19.2%-14.0%),

although not notably altered in subjects from Arms A or C (Table 1). The vaccination coverage among the 1992 to 1995 females was comparatively similar among the intervention Arms A and B (Figure 1).

### 3.2 | HPV seroprevalence, postvaccination vs prevaccination era

Among the subjects, the crude seroprevalence, P, of vaccine targeted HPV16 and 18 was notably high among all three intervention arms

**TABLE 3** HPV type-specific seroprevalence ratios comparing the seroprevalence in the postvaccination era, to that in the prevaccination era

		Seroprevalence ratios (95% CI)						
		Unvaccinated Finnish females aged under 23 years						
		First postvaccination vs prevaccination era			Second postvaccination vs prevaccination era			
HPV type		Arm A (n = 662 vs 1322)	Arm B (n = 602 vs 1289)	Arm C (n = 650 vs 1304)	Arm A (n = 585 vs 1322)	Arm B (n = 556 vs 1289)	Arm C (n = 561 vs 1304)	
Vaccine targeted	hr 16	0.76 (0.65-0.88)	1.16 (0.95-1.42)	0.96 (0.78-1.17)	0.83 (0.72-0.96)	1.03 (0.83-1.28)	1.07 (0.90-1.27)	
	18	0.78 (0.59-1.01)	0.92 (0.72-1.18)	0.81 (0.62-1.06)	0.95 (0.75-1.19)	1.01 (0.71-1.43)	0.98 (0.76-1.27)	
Nonvaccine targeted	lr 6	0.83 (0.68-1.02)	0.98 (0.81-1.19)	1.02 (0.87-1.21)	0.73 (0.61-0.86)	0.66 (0.49-0.90)	0.81 (0.69-0.96)	
	11	1.04 (0.72-1.50)	0.86 (0.61-1.22)	1.01 (0.72-1.43)	0.80 (0.55-1.15)	0.70 (0.46-1.07)	0.55 (0.33-0.89)	
	hr 39	0.99 (0.82-1.20)	1.19 (0.91-1.55)	1.05 (0.84-1.31)	1.08 (0.86-1.36)	0.93 (0.75-1.16)	1.14 (0.91-1.44)	
	51	1.02 (0.79-1.31)	1.06 (0.90-1.25)	1.03 (0.84-1.28)	0.88 (0.70-1.10)	0.98 (0.82-1.18)	0.91 (0.71-1.17)	
	56	0.83 (0.70-0.99)	1.06 (0.90-1.24)	0.95 (0.73-1.23)	0.81 (0.66-1.00)	0.80 (0.58-1.09)	0.73 (0.56-0.95)	
	58	0.78 (0.67-0.91)	1.03 (0.86-1.23)	0.89 (0.74-1.07)	0.61 (0.53-0.70)	0.66 (0.53-0.84)	0.66 (0.51-0.87)	
	59	0.99 (0.73-1.33)	1.13 (0.87-1.46)	1.12 (0.86-1.46)	0.99 (0.75-1.32)	0.86 (0.68-1.09)	0.85 (0.67-1.07)	
	66	0.85 (0.71-1.01)	0.93 (0.74-1.16)	0.96 (0.77-1.21)	0.82 (0.68-1.00)	0.85 (0.65-1.11)	1.16 (0.91-1.47)	
	68	0.80 (0.54-1.16)	1.02 (0.71-1.48)	0.99 (0.65-1.52)	1.10 (0.76-1.59)	1.54 (1.02-2.34)	1.36 (1.00-1.85)	
73	0.76 (0.60-0.96)	0.96 (0.75-1.23)	1.13 (0.96-1.33)	0.72 (0.55-0.93)	0.78 (0.56-1.08)	0.83 (0.59-1.17)		

Note: The prevaccination era is defined as 2005-2010, and the postvaccination era as 2011-2016, which is further divided into the first and second postvaccination eras of 2011-2013 and 2014-2016 respectively. Estimates are stratified by trial arm (*hr*, high-risk HPV type; *lr*, low-risk HPV type).

consistently above 15% for HPV16 and above 10% for HPV18. When comparing the postvaccination era to the prevaccination era, 2011-2016 to 2005-2010, respectively, the seroprevalence of the HPV16 and HPV18 was reduced (without overlapping 95% confidence intervals in the case of HPV16) in Arm A (from  $P_{\text{HPV16}} = 22.1\%$ , to  $P_{\text{HPV16}} = 17.4\%$  and from  $P_{\text{HPV18}} = 14.4\%$  to  $P_{\text{HPV18}} = 12.2\%$ ), no comparable reductions were observed in Arm B or C. Among the nonvaccine targeted HPV types the crude seroprevalence of HPV6, 56, 58, 66 and 73 was found to decrease in Arm A (from  $P_{\text{HPV6}} = 24.1\%$  to  $P_{\text{HPV6}} = 18.7\%$ ,  $P_{\text{HPV56}} = 17.9\%$  to  $P_{\text{HPV56}} = 14.8\%$ ,  $P_{\text{HPV58}} = 23.7\%$  to  $P_{\text{HPV58}} = 16.3\%$ ,  $P_{\text{HPV66}} = 17.3\%$  to  $P_{\text{HPV66}} = 14.4\%$  and from  $P_{\text{HPV73}} = 12.8\%$  to  $P_{\text{HPV73}} = 9.3\%$ ; Figure 3).

When comparing the postvaccination era to the prevaccination era among all the subjects, the smoking adjusted seroprevalence ratios of both HPV16 and 18 were reduced among Arm A only (Table 2A). Among the nonvaccine targeted HPV types, the PR was decreased for HPV6, 66 and 73 ( $PR_{\text{HPV6A}} = 0.78$ , 95% CI 0.67-0.92,  $PR_{\text{HPV66A}} = 0.83$ , 0.73-0.96 and  $PR_{\text{HPV73A}} = 0.74$ , 0.60-0.91), without any similar decrease in Arm C. In Arm B for the nonvaccine targeted HPV types the PR was decreased for HPV6, 11 and 73 ( $PR_{\text{HPV6B}} = 0.82$ , 95% CI 0.75-0.91,  $PR_{\text{HPV11B}} = 0.78$ , 0.60-1.01 and  $PR_{\text{HPV73B}} = 0.87$ , 0.76-1.00). The PR of HPV68 was found to increase (PR = 1.28, 95% CI 0.97-1.68) only among Arm B, albeit nonsignificantly so (Table 2A). When conducting sensitivity analysis to additionally take into account systematic error due to outcome misclassification HPV68 was found to be further increased (PR = 1.51, 95% CI 1.02-2.44; Table S1). Further sensitivity analysis stratified by age group, found the Arm B specific increase in HPV68 to be more prominent among the younger subjects aged 14 to 19 years old (PR = 1.62, 95% CI 1.01-2.60; Table S2).

When comparing the postvaccination era to the prevaccination era among all HSV-2 seropositive subjects (as a proxy of core-group

membership), the vaccine targeted HPV16 PR continued to be decreased in Arm A ( $PR_{16} = 0.64$ , 95% CI 0.50-0.81). Among the nonvaccine targeted types, no PRs were found to increase in Arm A. In Arm A, the PRs for HPV6, 66 and 73 were again all decreased ( $PR_{6A} = 0.61$ , 95% CI 0.43-0.87,  $PR_{66A} = 0.72$ , 0.53-0.98 and  $PR_{73A} = 0.45$ , 0.35-0.59), notably with the exception of HPV66 there were no similar decreases in Arm C. In Arm B, the PRs for HPV6, 66 and 73 were also decreased ( $PR_{6B} = 0.43$ , 95% CI 0.34-0.54,  $PR_{66B} = 0.76$ , 0.44-1.30 and  $PR_{73B} = 0.84$ , 0.57-1.24). However, only for HPV6 was the magnitude of the decrease not replicated in Arm C. Among the HSV-2 seropositive subjects of Arm B, the PR was found to be substantially increased solely for HPV68 ( $PR_{68} = 2.78$ , 95% CI 1.23-6.31; Table 2B).

When comparing the latest half of the postvaccination era to the prevaccination era, 2014-2016 to 2005-2010, among all subjects irrespective of HSV-2 seropositivity, no significant increases in nonvaccine target PRs were observed in Arm A. Among Arm B, the PR estimate for HPV68 was further increased ( $PR_{68} = 1.54$ , 95% CI 1.02-2.34). However, during this era, HPV68 PR was also increased among Arm C ( $PR_{68} = 1.36$ , 95% CI 1.00-1.85; Table 3) When conducting sensitivity analysis to account for additional systematic error, HPV68 was again found to be further increased in the second postvaccination era, but not significantly different to that found in Arm C (Table S3).

### 3.3 | Comparing HPV seroprevalence changes by trial arm

When comparing the within-arm PRs between the Arms A or B to Arm C, we found no notable increases in the nonvaccine HPV types'

ratios of seroprevalence ratios (RPRs; Figure S1). When comparing Arm B to Arm C core-groups, although the HPV68 RPR was increased, the confidence intervals overlapped the null (RPR = 1.98, 0.73-5.40), and for the latest subjects, the RPR approximated 1 (Figure S2, Table S4).

## 4 | DISCUSSION

Of all the nonvaccine targeted HPV types measured, only the seroprevalence of HPV68 was found to have increased in the post-vaccination era in the manner which would be expected if type replacement was occurring. This increase was only observed after girls-only vaccination, with concomitantly reduced HPV6/11 seroprevalence. The magnitude of the postvaccination era increase in HPV68 seroprevalence was particularly pronounced in the core-group (identified using HSV-2 seropositivity). Moreover, this increase was found to stem more from the later postvaccination years, from 2014 to 2016, as would be expected if this increase was as a result of type replacement.

When comparing this postvaccination vs prevaccination increase to that in the counterfactual control Arm C, this increase among Arm B was found to disappear, except in the core-group. This might suggest that the observed increase in Arm B may have been partially due to secular trends rather than type replacement. Furthermore, the core-group observations lacked statistical significance, meaning that the observed increase may have been due to chance.

Although the finding of increased HPV68 may be explainable due to aforementioned reasons other than type replacement, this possibility deserves comment. Previous modelling studies assuming that HPV types compete via the hosts immune system, have demonstrated that the occurrence of type replacement, and the ability to observe it at an early stage of the postvaccination era, is a trade-off between vaccine-induced cross-protection and naturally acquired cross-immunity.<sup>15</sup> HPV68 is from the alpha 7 species, and although phylogenetically related to HPV18 present in the bivalent vaccine, has not been shown following vaccination programs or clinical trials to be cross-protected by the vaccine.<sup>34</sup> Although a large degree of vaccine-induced cross-protection has been demonstrated against types phylogenetically related to vaccine targeted HPV16 and 18, alpha 9 and alpha 7 species, respectively, the vaccine has been much more successful at eliciting cross-neutralising antibodies to HPV types from alpha 9, than it has to HPV types from alpha 7.<sup>35</sup> From the alpha 7 species, only HPV45 has been shown to be cross-protected by the bivalent vaccine.<sup>13</sup> Thus, the HPV68 increase will likely not be mitigated by vaccine-induced cross-protection. Furthermore, the fact that the observed increase in HPV68 after girls-only vaccination stems more from the second postvaccination era, is in line with a proposed honeymoon period postvaccination before type replacement might occur.<sup>15</sup>

We noted a decrease in both the occurrence of low-risk type HPV6, HPV 66 and the possibly high-risk type HPV73. This reduction in HPV6 was found to exactly follow the patterns that would be

expected if the bivalent vaccine had induced HPV6 herd effect; the observed reduction was the greatest postgender-neutral vaccination and when comparing to the control Arm C was not explainable due to secular trends. HPV6 is a very common low-risk HPV type, responsible for a large proportion of genital warts, and not phylogenetically related to either of the vaccine-targeted types. Nevertheless, this finding of a possible HPV 6 herd effect postbivalent HPV vaccination, is consistent with previous findings of bivalent vaccine efficacy against HPV6,<sup>36</sup> reported postvaccine era reductions in genital warts when using the bivalent vaccine,<sup>37,38</sup> and also with findings of HPV6 specific vaccine-induced cross-neutralising antibodies among individuals vaccinated with the bivalent HPV vaccine.<sup>35</sup> The finding of decreased HPV73, however, is unexpected. The majority of previous studies monitoring the HPV type distribution postbivalent HPV vaccination via PCR methodology have either not measured HPV73 at all or have been unable to distinguish transitory infection with HPV68 to that due to HPV73, due to limitations of the laboratory method used. This finding of a possible herd effect against HPV73 is therefore reassuring; although HPV73 was officially classified as a possibly high-risk type in the last published version of the IARC monograph pertinent to HPV,<sup>4</sup> a study conducted since its publication found HPV73 to be causally associated with the development of invasive cervical cancer.<sup>39</sup> HPV73 is from the alpha 11 species group, which is of particular interest given that the alpha 11 species group is phylogenetically close to the alpha 9 species, and the degree of cross-protection is correlated to the phylogenetic distance to the vaccine types.<sup>40</sup> Contrary to this, the observed decrease of HPV66 in Arm A was unexpected. Previous studies have not documented any decrease in HPV66 following the induction of the bivalent HPV vaccine. In several such studies, HPV66 was not included in the laboratory assay,<sup>41,42</sup> and where HPV66 was evaluated, there was no notable vaccine efficacy observed against a HPV infection endpoint.<sup>43,44</sup> Thus, the currently observed decrease in HPV66 necessitates further study before any causal relationship may be asserted, to guard against a chance finding among the multiple HPV type comparisons which are commonplace in such HPV type replacement studies.

Even with a decade of follow-up, our study may still be limited in its ability to evaluate HPV type replacement. A recent modelling study found that there may be a honeymoon period of 10 years after the start of HPV vaccination in a population, before HPV type replacement starts to occur.<sup>15</sup> However, this is only considering the scenario where prevaccination competition occurs via naturally acquired cross-immunity,<sup>15</sup> thus if type competition occurs via another mechanism, such as for resources (eg, competition for available micro-abrasions), then it may be that this honeymoon period either does not apply or is altered. Therefore, whether or not our survey is limited by the follow-up may be subject to the biology of HPV type competition.

Furthermore, our study may also suffer from bias due to misclassification of the outcome, cumulative HPV infection. As previously described,<sup>22</sup> when measuring the occurrence of HPV infection in a population, when using either HPV DNA measures or serological measures among unvaccinated individuals, both methods suffer from misclassification of the outcome. When using transitory DNA positivity

as a marker of current infection, the investigator shall also incorrectly identify a proportion of individuals as HPV positive whom have only a deposition of transient HPV and not an actual infection.<sup>45</sup> When using HPV serology, on the other hand, it allows for the identification of those individuals who have had true persistent infections, and is a measure of cumulative HPV infection exposure.<sup>46</sup> Serum IgG antibodies induced by natural infection specific to HPV types have previously been shown to be stable over several years of follow-up among women.<sup>47</sup> However, this method will also incorrectly identify a proportion of individuals as negative who have previously had a HPV infection but have not seroconverted; among a sample of Swedish women with clinically confirmed HPV16 infections only 65% were found to be HPV16 seropositive.<sup>48</sup> Therefore, by using type-specific HPV serology as a measure of cumulative infection our comparative measures of HPV occurrence are likely deviated towards the null.

There are many difficulties in designing a study with the ability to evaluate type replacement of any kind. The community-randomised trial design of our study with both pretrial and posttrial outcome measurements is best placed to evaluate type replacement and avoid many of these common problems.<sup>15</sup> The pretrial and posttrial measurements in the counterfactual control Arm C, makes it possible to distinguish type replacement from secular trends in nonvaccine HPV occurrence, and the community-wise vaccination where entire birth cohorts of early adolescents were identified and invited to participate in the trial, mimics the expected selective pressure to HPV ecology after the application of a national vaccination program. Further to which, the comparison of HPV unvaccinated females in the prevaccination and postvaccination eras allows for the evaluation of type replacement among the population subject to the indirect effects of community-wise vaccination.

Although our study is highly generalizable to the wider pregnant Finnish population under the age of 23 due to the population-based nature of the study, it may be limited in its generalisability to all females under the age of 23 years old. Although the prevalence of maternal smoking (an indicator of general risk-taking behaviour) is high in our study population, it is almost identical to that found in previous studies of pregnant females of similar age over for the total population of Finland.<sup>49</sup> However, it is likely that our study population has above and below average sexual risk-taking behaviours compared to the general population given that the average age of first pregnancy in Finland is currently 29-years-old.<sup>50</sup> Despite the presence of our control Arm C to control for secular trends, our study still may not have been able to completely distinguish the magnitude of the increase in HPV68 due to type replacement from that due to secular trends, for example, if the parallel trend assumption between the Arms does not hold. Finally, although our study with moderate vaccination coverage may mimic typical vaccination coverages achieved in many national vaccination programs, it is limited in its transportability to scenarios with greater vaccination coverage.

In conclusion, no clear indications of type replacement were found, as of yet. Possible increases in HPV68 after girls-only vaccination may have resulted from secular trends. Continued monitoring in the postvaccination era to confirm or refute possible HPV type

replacement by HPV68 and all other nonvaccine targeted HPV types is necessary.

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## CONFLICT OF INTEREST

M. L. has previously received grants from Merck & Co. Inc. and the GSK group of companies through his then employer (The University of Tampere).

## ETHICS STATEMENT

At the time of sample donation, the pregnant females comprising the FMC gave their informed consent for the future use of their samples for research purposes. Ethical permission for the community randomised trial was granted in 2007 from the Pirkanmaa Hospital District Ethical Review Board (R07113M 14.6.2007).

## DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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