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HIV-STIs

Post-immunisation monitoring of HPV vaccine-induced seroprevalence in England 2010 to 2013

Background

Seroconversion occurs following an estimated 50-70% of incident natural human papillomavirus (HPV) infections in women [1-4] and natural infection often elicits only a weak antibody response. Conversely, vaccination induces seroconversion in ~100% of HPV-naïve recipients and generally results in far higher antibody concentrations than those following natural infection [5,6]. As such, serological assays which provide a quantitative measure of the level of HPV type-specific antibodies can be used to estimate HPV vaccination coverage.

Public Health England (PHE)'s monitoring of HPV seroprevalence (as part of work to monitor and evaluate the National HPV Immunisation Programme) has begun with a study of young women in the first birth cohorts to be offered HPV immunisation, primarily to compare vaccine-induced seroprevalence to nationally reported coverage data. The first results from this surveillance have been published previously with data from 2,146 specimens collected between 2010 and 2011 [7]. We report here updated findings with results from 3,772 specimens collected up to 2013.

Methods

Residual serum specimens were collected for 15-19 year old females from the PHE Seroepidemiology Unit (SEU). SEU specimens are collected from individuals attending for microbiological and/or biochemical tests. Serum samples were submitted with data on gender, age at collection and year of collection from fourteen laboratories in England. Laboratories were asked to identify, if possible, any specimens collected via Genitourinary (GU) Medicine clinics (defined as No, Yes or Not known). Specimens collected from 2010 to 2013 are included in this analysis.

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Where date of birth was available, this was used to generate the age and calendar year that HPV vaccination would have been offered: this was available for 2355/3772 (62.4%) of women. For the remainder, with age in years available, likely year of eligibility for HPV vaccination was estimated. Specimens collected in January-March following the due date of first vaccine dose were excluded in order to study seroprevalence after, not during, the scheduled full course of vaccination.

Specimens were tested for antibodies to HPV types 16 and 18 using a type-specific ELISA. Testing was performed at the PHE Vaccine Evaluation Unit (VEU), Manchester. Specimens were considered to be seropositive above cut-offs determined previously with this assay: 19 and 18 ELISA units per millilitre (EU/mL) for HPV 16 and 18, respectively.

Methods to determine vaccine-induced seropositivity were as previously described [7]. In brief, each result was classified as “low”, “moderate” or “high” based on the concentration of HPV antibodies for HPV16 and HPV18. Specimens were then categorised as (i) “probable” vaccine-induced seropositivity if seropositive for both types with high concentration for at least one type or moderate concentrations for both types, (ii) “probable” natural infection if seropositive for one type only, (iii) “possible” natural infection or vaccine induced seropositivity if low seropositivity for both types or low seropositivity for one type and moderate for the other. Antibody concentrations are presented as geometric mean concentrations (GMCs) among seropositive specimens.

Routinely published data on HPV vaccine coverage in England has been reported by academic year. To compare these data with seroprevalence we estimated coverage by year of age and calendar year.

Results

A total of 4,045 specimens had a valid result for type-specific HPV antibodies for both HPV types 16 and 18. Excluding 323 samples which were collected in the January to March of the year following the due date of first vaccine dose; 3,722 specimens were included in this analysis (1205, 941, 952 and 674 collected in 2010, 2011, 2012 and 2013, respectively). The mean age of women providing a specimen was 17.8 years (SD 1.42 years). Overall, just under one-third (32.4%) of all specimens were identified as coming from a GU setting although this was not known for the majority of other specimens (64.1%): specimens from a known non-GU setting had higher seroprevalence (p=0.01 for vaccine-induced seropositivity). Table 1 shows the demographics of all eligible women alongside the proportion seropositive for at least one HPV type.

Table 1. Seropositivity by clinical setting, age and laboratory sending specimen

	Number with valid result	Proportion seropositive for HPV 16 and/or 18	Proportion seropositive for HPV 16 and 18	Vaccine-induced seropositivity
	n	n (%)	n (%)	n (%)
Total	*3,772*	*2,861 (75.8)*	*2,638 (69.9)*	*2,472 (65.5)*
Genito-urinary Medicine (GUM) clinic setting				
Yes	1,206	928 (76.9)	852 (70.6)	798 (66.2)
No	149	126 (84.6)	119 (79.9)	114 (76.5)
Unknown	2,417	1,807 (74.8)	1,667 (69.0)	1,560 (64.5)
Age specimen taken				
15 years	643	527 (82.0)	512 (79.6)	492 (76.5)
16 years	729	600 (82.3)	573 (78.6)	547 (75.0)
17 years	590	464 (78.6)	433 (73.4)	401 (68.0)
18 years	957	713 (74.5)	645 (67.4)	600 (62.7)
19 years	853	557 (65.3)	475 (55.7)	432 (50.6)
Laboratory[1]				
North East				
Newcastle	361	305 (84.5)	280 (77.6)	258 (71.5)
North West				
Manchester	577	443 (76.8)	413 (71.6)	395 (68.5)
Yorkshire and The Humber				
Leeds	946	729 (77.1)	671 (70.9)	624 (66.0)
East Midlands				
Cambridge	166	116 (69.9)	107 (64.5)	100 (60.2)
Leicester	347	285 (82.1)	277 (79.8)	264 (76.1)
West Midlands				
Birmingham	81	51 (63.0)	43 (53.1)	41 (50.6)
London				
Barts and The London	230	134 (58.3)	121 (52.6)	108 (47.0)
St George's Hospital	167	99 (59.3)	83 (49.7)	77 (46.1)
PHL London[2]	139	96 (69.1)	82 (59.0)	76 (54.7)
South Central				
Southampton	103	85 (82.5)	79 (76.7)	74 (71.8)
South East				
Brighton[3]	49	30 (61.2)	25 (51.0)	24 (49.0)
South West				
Bristol	69	58 (84.1)	55 (79.7)	51 (73.9)
Exeter	510	412 (80.8)	384 (75.3)	363 (71.2)
Gloucester	27	18 (66.7)	18 (66.7)	17 (63.0)

1: Proportion seropositive for each laboratory are age and year-standardised

2: PHL = Public Health Laboratory; specimens collected in 2012 and 2013 only

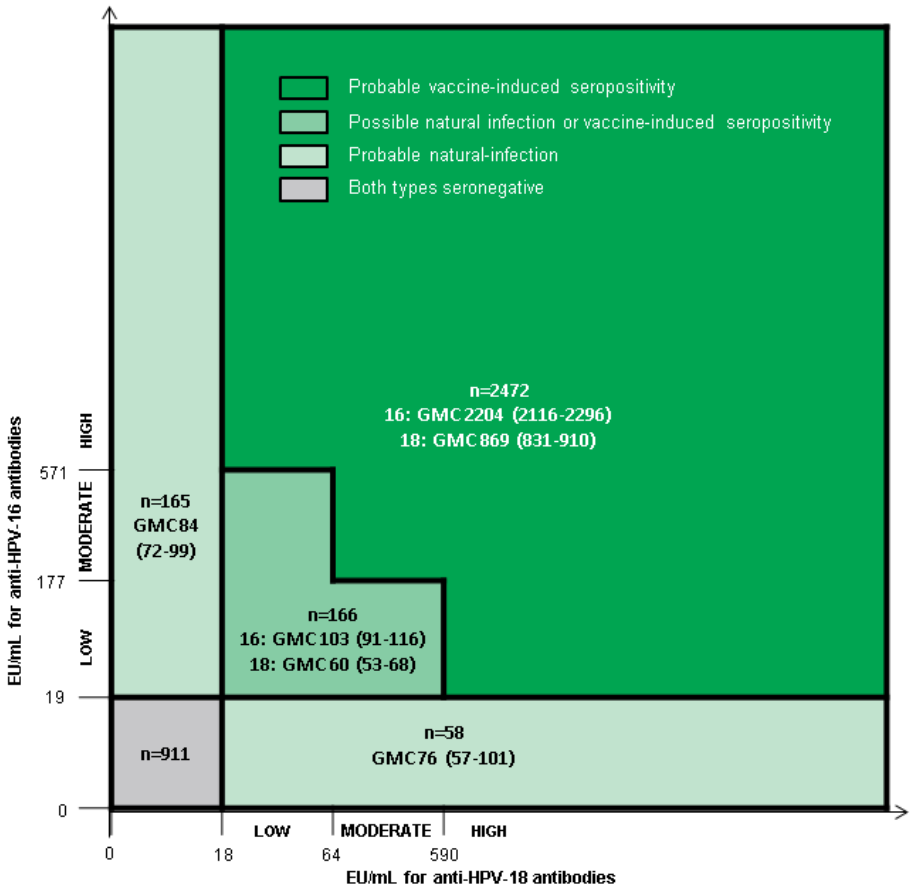
3: Specimens collection in 2010 only

A total of 69.9% (2,638/3,772) of specimens were seropositive for both types HPV16 and HPV18. Seropositivity for HPV16 only and for HPV18 only was found in 4.4% (165) and 1.5% (58) of specimens respectively (table 2; figure 1). Antibody concentrations were generally far higher for specimens seropositive for both HPV types than amongst those seropositive for only one type (median 2017.5 EU/ml vs 70 EU/ml for HPV16 and 804.5 EU/ml vs 59 EU/ml for HPV18) (table 2).

Table 2. Antibody concentrations for types HPV16 and HPV18

		HPV type 16		HPV type 18	
HPV type	n (%)	Median EU/mL (IQR)	95% range	Median EU/mL (IQR)	95% Range
Both types negative	911 (24.2%)	–	–	–	–
16 negative, 18 positive	58 (1.5%)	–	–	59 (30-172)	18 – 590
16 positive, 18 negative	165 (4.4%)	70 (37-156)	23-571	–	–
Both types positive	2,638 (69.9%)	2,017.5 (929-4200)	177 – 11,675	804.5 (343-1,756)	64 – 5,460
Total	3,772 (100%)				

Figure 1. Classification of vaccine-induced seropositivity (n=3,772)



Using the range of concentrations for types 16 and 18 seropositives we classified each result as, (i) "high" seropositivity if the result was above the 95% range of concentrations among those with a single antibody (i.e. unusually high for presumed largely naturally infected); (ii) "low" seropositivity as below the lower 95% range of concentrations among those seropositive for both HPV types (i.e. unusually low for dual seropositivity, presumed largely immunised); (iii) "moderate" seropositivity as between these two values.

Vaccine-induced seropositivity was highest in the younger ages with higher expected vaccine coverage (table 3). This finding was consistent in sub-analyses by region (data not shown). The overall proportion of females with probable vaccine-induced seropositivity was 66% (2,472/3,772) and 4.4% (166/3,772) with possible natural infection or possible vaccine-induced seropositivity. The proportion of females with vaccine-induced seropositivity was slightly lower than the reported three-dose coverage for 15 and 16 year olds but higher at older ages (table 3 and figure 2).

Table 3. Seropositivity for HPV 16 and 18 amongst all specimens tested for both HPV types, by age

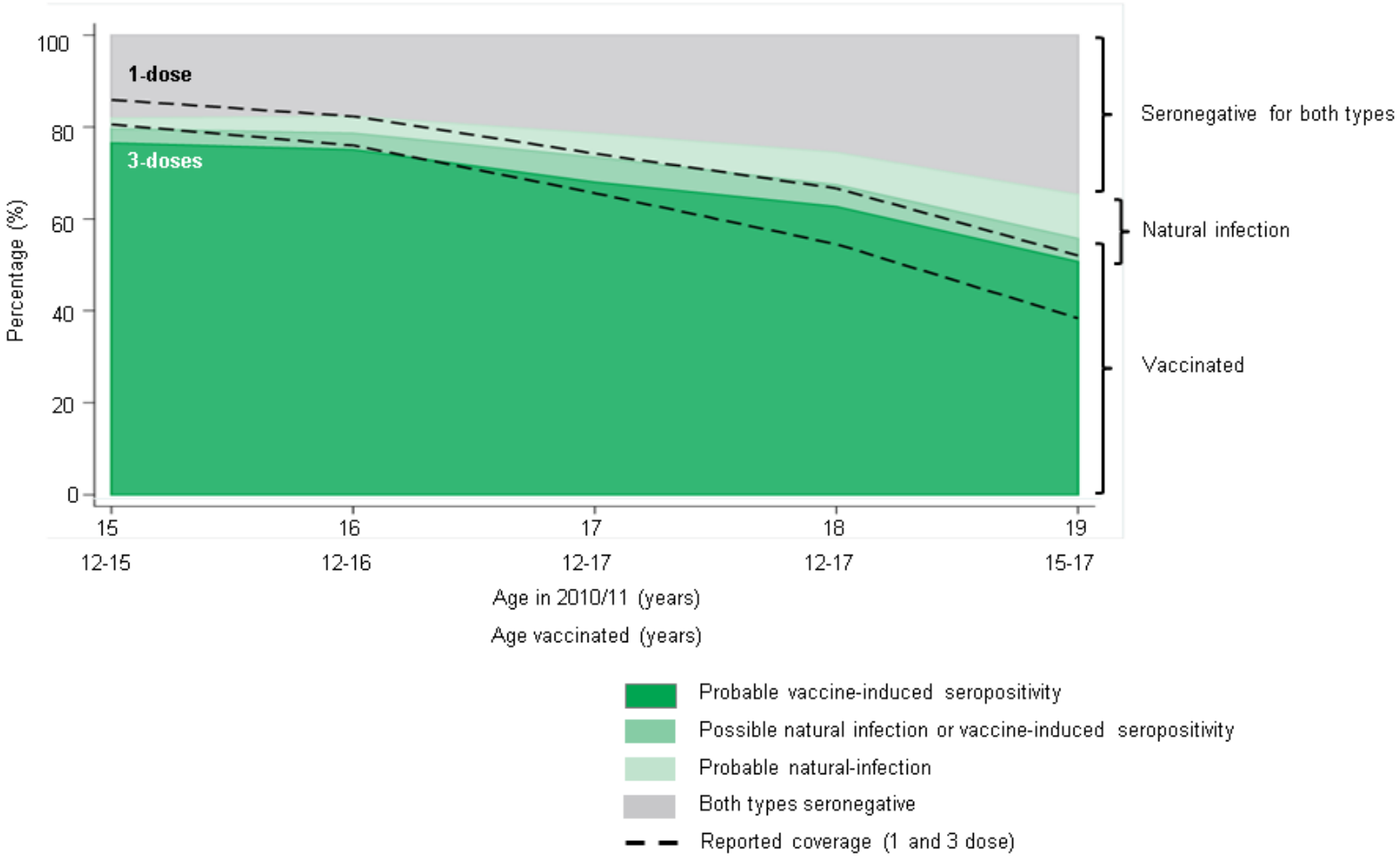
	Age in years					
HPV type	15	16	17	18	19	*Total*
Both types negative	18.0% (116)	17.7% (129)	21.4% (126)	25.5% (244)	34.7% (296)	*24.2% (911)*
Natural infection seropositivity:						
- Probable 18 only	1.1% (7)	1.2% (9)	1.0% (6)	2.0% (19)	2.0% (17)	*1.5% (58)*
- Probable 16 only	1.2% (8)	2.5% (18)	4.2% (25)	5.1% (49)	7.6% (65)	*4.4% (165)*
- Probable 18 or 16	2.3% (15)	3.7% (27)	5.3% (31)	7.1% (68)	9.6% (82)	*5.9% (223)*
- Probable and possible	5.4% (35)	7.3% (53)	10.7% (63)	11.8% (113)	14.7% (125)	*10.3% (389)*
Vaccine-induced seropositivity:						
- Probable	76.5% (492)	75.0% (547)	68.0% (401)	62.7% (600)	50.6% (432)	*65.5% (2,472)*
- Probable and possible	79.6% (512)	78.6% (573)	73.4% (433)	67.4% (645)	55.7% (475)	*69.9% (2,638)*
Expected 1-dose (national)	86.0%	82.3%	74.2%	66.7%	52.1%	-
Expected-3-dose (national)	80.6%	76.0%	65.6%	54.5%	38.4%	-

The GMCs amongst all women and those with probable vaccine-induced seropositivity group declined slightly with age (table 4). Furthermore, in women with a known date of birth, the GMCs declined after the first year but then seemed to remain stable at a level far higher, on average, than the GMCs for those seropositive for only one HPV type (figure 3).

Table 4: Geometric mean concentrations (GMCs; 95% CI) of EU/mL for HPV16 and HPV18, by age

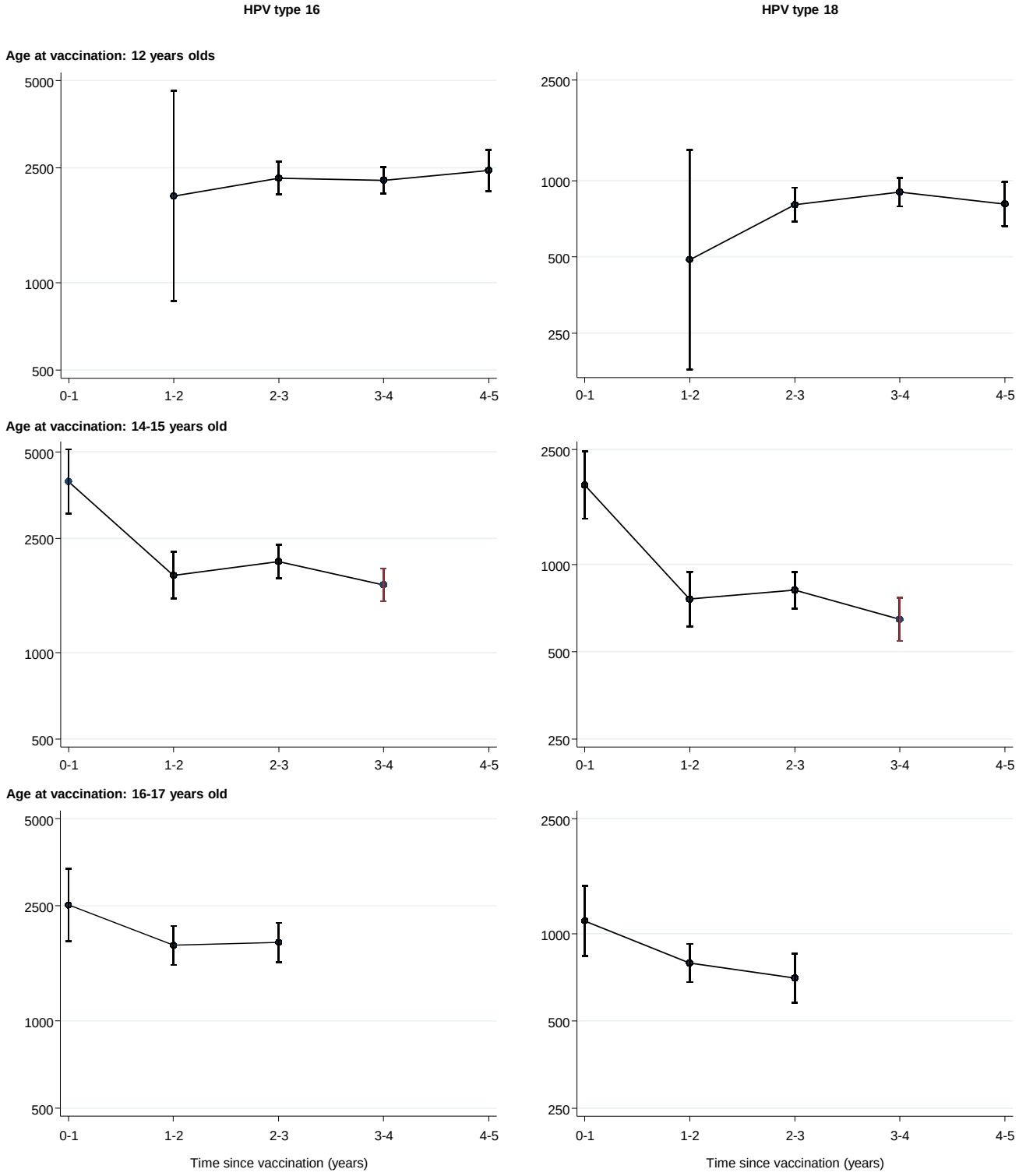
	Age in years				
	15	16	17	18	19
Type 16					
Seropositive	2,207 (1,979-2,461)	1,840 (1,661-2,037)	1,424 (1,246-1,628)	1,357 (1,213-1,517)	1,042 (911-1,193)
Vaccine-induced seropositive	2,632 (2,402-2,883)	2315 (2,134-2,513)	2,078 (1,871-2,309)	2,087 (1,920-2,269)	1,929 (1,750-2,125)
Type 18					
Seropositive	857 (766-959)	792 (714-878)	664 (585-753)	631 (569-699)	589 (520-668)
Vaccine-induced seropositive	993 (896-1,100)	925 (841-1,017)	819 (730-919)	814 (744-891)	799 (715-894)

Figure 2. Published HPV vaccine coverage and vaccine-induced seropositivity, by age (n=3,772)



"Probable" vaccine-induced seropositivity defined as seropositive for both types with high concentration for at least one type or moderate concentrations for both types. "Probable" natural infection as seropositive for one type only. "Possible" natural infection or vaccine-induced seropositivity defined as low seropositivity for both types or low seropositivity for one type and moderate for the other

Figure 3. Geometric mean concentrations (GMCs; EU/mL) and 95% CI for HPV16 and HPV18 among those with probable vaccine-induced seropositivity (restricted to women with a known date of birth who would have been eligible for vaccination as part of the national immunisation programme (n=1,569)



Discussion

We have previously reported that serological surveillance confirms high vaccine coverage of the HPV vaccination programme in young females in England, particularly in those offered the vaccine at younger ages, but that there was a slightly higher proportion with vaccine-induced seropositivity compared to reported three-dose coverage in females offered HPV vaccination at an older age suggesting that three-dose coverage in the catch-up cohorts could be higher than reported and/or that two-dose coverage at these ages is associated with high antibody responses. These updated analyses strengthen these conclusions. In addition, we demonstrate that whilst geometric mean antibody concentrations declined immediately after vaccination, levels then remained fairly stable up to five years post-vaccination. Furthermore, the average antibody concentrations were still far greater than antibody concentrations following a natural HPV infection.

Vaccine status of women in this study is unknown which leads to two important limitations. Firstly, vaccine-induced seropositivity can't be compared to recorded vaccination status, hence we must assume that these women are representative of the general population with similar HPV vaccination coverage to national reported data. Residual serum specimens for this surveillance are taken from females attending for diagnostic and screening tests. No additional demographic data are collected on social deprivation, education, ethnicity or other factors which may be associated with vaccine uptake. However, everyone in England has free access to health care which reduces the potential bias associated with health-seeking behaviour and previous studies have suggested that results are comparable for other vaccines [8]. Secondly, measuring changes in natural infection among unvaccinated women compared to similar surveys conducted prior to the introduction of vaccination would allow us to consider if there is evidence of a herd protection effect. However, a limitation of this analysis was that it wasn't possible to accurately distinguish between women with a natural infection and women who have been vaccinated.

Among those vaccinated between 14 to 17 years of age, these results show initial waning of antibody concentrations immediately following vaccination and then stabilisation, which is fairly consistent with results from clinical trials [5]. It wasn't possible to consider waning after vaccination in the routinely vaccinated cohorts as sera from 12-14 years olds were not included in this analysis. Whilst the level of protection required to prevent HPV infection and related disease is not known, the plateau of antibody concentrations is still far higher than those seen with a natural infection for all ages. As such, annual monitoring may not be essential but periodic surveillance to monitor that antibody concentrations are remaining high in the general population could be valuable, and to check antibody concentrations in

recipients of the two dose schedule in due course. Future studies should also consider variations in the proportion of women with vaccine-induced seropositivity from different subgroups which will be required to accurately monitor of the impact of HPV vaccination.

Conclusion

These data add to previous data confirming high coverage of HPV vaccination in England but with some potential under-reporting of vaccination of older females and/or a potential protective effect of receiving fewer than three doses. This updated analysis provides data on antibody responses up to five years post-vaccination. Whilst there is some evidence of slight declines in antibody concentrations over time since vaccination, these still remain far higher than antibody concentrations following a natural infection.

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