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Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: an ongoing cross-sectional study

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ABSTRACT

Objectives: The human papillomavirus (HPV) immunisation programme in England was introduced in 2008. Monitoring changes in type-specific HPV prevalence allows assessment of the population impact of this vaccination programme.

Methods: Residual vulva-vaginal swab specimens were collected from young sexually active women (aged 16–24 years) attending for chlamydia screening across England. Specimens were collected between 2010 and 2013 for type-specific HPV-DNA testing. HPV prevalence was compared to a similar survey conducted in 2008 prior to the introduction of HPV vaccination.

Results: A total of 7321 specimens collected in the postvaccination period, and 2354 specimens from the prevaccination period were included in this analysis. Among the individuals aged 16–18 years, with an estimated vaccination coverage of 67%, the prevalence of HPV16/18 infection decreased from 17.6% in 2008 to 6.1% in the postvaccination period. Within the postvaccination period, there was a trend towards lower HPV16/18 prevalence with higher vaccination coverage and increasing time since vaccine introduction from 8.5% in the period 2–3 years postvaccination to 4.0% in the period 4–5 years postvaccination. The prevalence of HPV31 reduced from 3.7% in the prevaccination period to 0.9% after vaccine introduction, although this no longer reached statistical significance after additional consideration of the uncertainty due to the assay change. Smaller reductions were seen in the individuals aged 19–21 years with lower estimated vaccination coverage, but there was no evidence of a reduction in the older unvaccinated women. Some overall increase in non-vaccine types was seen in the youngest age groups (ORs (95% CI); 1.3 (1.0 to 1.7) and 1.5 (1.1 to 2.0) for individuals aged 16–18 and 19–21 years, respectively, when adjusted for known population changes and the change in assay) although this should be interpreted with caution given the potential unmasking effect.

Conclusions: These data demonstrate a reduction in the HPV vaccine types in the age group with the highest HPV vaccination coverage.

Strengths and limitations of this study

- We conducted human papillomavirus (HPV) surveillance among a large number of young women attending for chlamydia screening, with HPV type-specific testing performed for almost 10,000 women.
- The large sample size of this study has allowed us to consider the population impact of the bivalent HPV vaccine against the two vaccine types, and against cross-protective HPV types.
- We demonstrate continued decreases in the prevalence of vaccine-targeted HPV types over time up to 4 years after the introduction of the bivalent vaccination programme.
- Analyses compare data from repeat cross-sectional surveys. Therefore, unrecorded changes in the population characteristics may have resulted in a change in HPV prevalence which is unrelated to HPV vaccination.

INTRODUCTION

Persistent infection with a high-risk (HR) human papillomavirus (HPV) type is a necessary cause of cervical cancer, and has been shown to be associated with other cancers in men and women.[1 2] Two of these HR-HPV types, HPV16 and HPV18, are present in around 70–80% of cervical cancers.[3 4] Infection with low-risk (LR) HPV6 or HPV11 has been shown to be associated with the vast majority of genital warts.[5]

HPV vaccination of young females has been introduced widely in developed countries as well as in some developing countries[6] since 2007, using the first two licensed vaccines (a bivalent HPV16/18 vaccine and quadrivalent HPV6/11/16/18 vaccine). In late 2008, the UK began providing HPV vaccination, free at the point of delivery, routinely to 12-year-old females, and catch-up vaccination to females up to and including 17-year-olds. The bivalent vaccine was offered until September 2012 when the programme changed to offer the quadrivalent vaccine. Throughout the UK, over 80% of females eligible for routine vaccination each year have completed the three-dose course.[7–9] Three-dose coverage within the

catch-up ages has been lower, with average coverage of 73% for individuals aged 14–15 years, and 45% for 16–17 years,[7] although this is still higher than in most other countries.[10–12]

In 2013, we reported findings from our surveillance of type-specific HPV infections in sexually active young females in England, showing evidence of substantially lower HPV16/18 prevalence in the first 4000 postvaccination period specimens tested compared with prevaccination prevalence.[13] Reductions in the prevalence of HPV16/18 following the introduction of HPV vaccination have also been shown in Australia,[14] the USA,[15–17] Scotland[18] and Sweden.[19]

Some cross-protection against non-vaccine HR-HPV types closely related to HPV16/18 has been demonstrated in clinical trials of both vaccines (specifically, HPV31, HPV33 and HPV45 for the bivalent vaccine, and HPV31 for the quadrivalent vaccine),[20–22] and has been observed for the bivalent vaccine by ongoing surveillance of young women undergoing cervical screening in Scotland.[18] Ongoing surveillance for changes in the prevalence of other non-vaccine HPV types is also prudent. These changes could result from vaccination due to cross-protection against non-vaccine HR-HPV types (ie, causing decreases in prevalence) or due to type replacement (ie, causing increases in prevalence).

We report further findings from our ongoing HPV surveillance (now over 7000 postvaccination specimens) in our high-coverage population, including changes in vaccine and non-vaccine types. We aimed to determine to what extent any such observed changes were likely to have resulted from vaccination, rather than be due to methodological reasons (eg, assay performance, unmasking), or a result of other factors such as changes in sexual behaviour over time.

METHODS

The methods of specimen selection, collection and testing, and the characteristics of the study population have been described previously.[13 23] Briefly, residual vulva-vaginal swab specimens were collected via 10 laboratories from young women aged 16–24 years undergoing chlamydia screening at general practice, community and sexual health services (CaSH, otherwise known as family planning), and youth clinics. Residual specimens were all sent for HPV testing at the Virus Reference Department laboratory at Public Health England (PHE). In England, chlamydia screening is recommended for all sexually active men and women under 25 years old annually, and on partner change, irrespective of symptoms or perceived risk. Demographic data were reported separately and linked to the specimens received at the PHE Centre for Infectious Disease Surveillance and Control. Prior to testing for HPV DNA, specimens were unlinked from any patient-identifiable data and anonymised. This study was reviewed and approved by the South East Research Ethics Committee (REC reference: 10/H1102/7). Individual patient consent was not required as this study tested anonymised specimens (with no patient-identifiable data) as part of Public Health Surveillance conducted to monitor the HPV vaccination programme.

Prevaccination-period specimens were collected between January and September 2008, prior to the introduction of the national HPV vaccination programme in England. Postvaccination-period specimens were collected between October 2010 and April 2013, and divided into two periods, 2–3 (ie, 2010–2011) and 4–5 years (ie, 2012–2013) postvaccination.

Postvaccination specimens were tested for type-specific HPV DNA to detect 13 HR types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), five possible HR types (HPV26, 53, 70, 73 and 82) and two LR types (HPV6 and 11) using an in-house multiplex PCR and Luminex-based genotyping test with pyruvate dehydrogenase (PDH) detection for sample integrity.[24] Prevaccination specimens were tested by Hybrid Capture 2 (HC2) HPV DNA test using the Combined Probe Cocktail Method to detect HR and possible HR types (as above) and five LR types (6, 11, 42, 43 and 44) and genotyped by the Linear Array HPV Genotyping (LA) test (Roche Molecular Systems) if HC2 positive.

HPV prevalence was calculated for each individual HPV type. We also calculated combined HPV prevalence, restricted to types included in the prevaccination and postvaccination assays, for (1) any HR-HPV type; (2) the HR-HPV types included in the current vaccines: HPV16 and/or 18; (3) the additional HR-HPV types included in the nonavalent HPV vaccine[25]: HPV31, 33, 45, 52 and/or 58; (4) the HPV types for which there is some evidence of cross-protection from clinical trials: HPV31, 33 and/or 45 and (5) the non-vaccine HR-HPV types (ie, HR types not including HPV16 or 18). Changes in prevalence between the prevaccination and postvaccination (combined) periods were compared using ORs calculated using a logistic regression model. Trends over time were assessed by including three time periods (prevaccination, 2–3 years postvaccination, 4–5 years postvaccination) as an ordered continuous variable. Adjusted ORs were calculated adjusting for age, testing venue type and chlamydia positivity (as a marker for sexual behaviour). To account for the change in assay between the prevaccination and postvaccination periods, we used type-specific sensitivity and specificity estimates from a validation study (428 prevaccination specimens, retested through the postvaccination testing system[13]). The logitem command in Stata was used to adjust for the different sensitivity and specificity of the assay used in the prevaccination period. This command performs logistic regression when the binary outcome is measured with uncertainty. This adjustment did not account for the uncertainty surrounding the sensitivity and specificity estimates, hence, bootstrapping techniques were used to incorporate this additional uncertainty to the SEs of the ORs. A similar statistical model

to adjust for assay change was not available for use with prevalence ratios (PR). However, PRs adjusted for age, testing venue type, and chlamydia positivity were also calculated using a log binomial model and the results compared with the equivalent ORs.

In order to further address concerns about changes in prevalence of HPV in the postvaccination period unrelated to vaccine introduction (eg, changes in sexual behaviour not addressed by adjustment of chlamydia positivity or residual changes in assay sensitivity), we also compared prevaccination and postvaccination type-specific prevalence when restricted to specimens with at least one HR-HPV type detected. This enabled assessment of changes in the relative, rather than absolute, frequency of specific HR types. To give a simple example, if prevaccination specimens comprised 20% HR type positivity overall (10% prevalence of type 31 and 10% prevalence of type 33), and postvaccination specimens comprised 30% HR type positivity (15% prevalence of type 31 and 15% prevalence of type 33), the absolute frequency of each type would increase postvaccination. However, the relative prevalence of each type within the HR-HPVs positives would remain the same.

Vaccination coverage by age and time period was derived from published data.[7–9 26]

RESULTS

Demographics and characteristics

Results were analysed from 2354 prevaccination specimens and 7321 postvaccination specimens: 3602 (49.2%) from 2–3 years postvaccination, and 3719 (50.8%) from 4–5 years postvaccination. The characteristics of study participants were similar in the prevaccination and postvaccination periods (table 1), except there were more specimens from women of non-white ethnic groups, and fewer specimens collected from youth clinics in the postvaccination collection (7.3% vs 17.6%, and 24.1% vs 3.1%, respectively). Furthermore, two laboratories, Leeds and Lewisham, included in only the postvaccination period, had notably higher chlamydia positivity rates than the other laboratories (22.4% and 8.4%, respectively). Data from these laboratories were excluded in sensitivity analyses. In the postvaccination period, the estimated vaccination coverage in the surveillance population, based on nationally reported data, was 67.2%, 30.7% and 0.6% for individuals aged 16–18, 19–21 and 22–24 years, respectively (table 2 for estimates by time period).

HR HPV16 and/or 18 infection

In the youngest age group (16–18 years), the prevalence of HPV16/18 was 17.6% in the prevaccination period compared to 8.5% in the period 2–3 years postvaccination, and 4.0% 4–5 years postvaccination (p value for trend <0.001; table 2 and figure 1). This corresponds to an overall reduction of 66% comparing the prevaccination prevalence to the combined postvaccination prevalence. A trend was also seen in individuals aged 19–21 years with a prevaccination prevalence of 16.9% compared to 14.2% in the period 2–3 years postvaccination, and 8.7% 4–5 years postvaccination (p value for trend <0.001; combined reduction between the prevaccination and postvaccination periods of 31%). However, there was no decrease in the prevalence of HPV16 and/or HPV18 in the oldest age group, who were largely unvaccinated. There was a slight decrease in HPV18 infection in the oldest age group, but this difference was no longer seen once adjustment was made for changes in population and HPV assay (data not shown).

The adjusted ORs for the postvaccination periods (combined) compared with the prevaccination period were 0.3 (95% CI 0.2 to 0.4), 0.6 (95% CI 0.5 to 0.9) and 1.1 (95% CI 0.8 to 1.7) for individuals aged 16–18, 19–21 and 22–24 years, respectively (table 3).

HR HPV31, 33 and/or 45 infection (cross-protective HPV types)

The prevalence of HPV31, 33 and/or 45 among the individuals aged 16–18 years was 8.4% in the prevaccination period, 6.9% in the period 2–3 years postvaccination, and 5.8% 4–5 years postvaccination. After adjusting for demographics and the change in HPV assay, the adjusted OR postvaccination (combined) was 0.9 (95% CI 0.5 to 1.5), p value=0.58 (tables 2 and 3). The prevalence of HPV31 in this age group reduced from 3.7% in the prevaccination period to 0.9% in the combined postvaccination period. This reduction did not reach statistical significance after adjustment for the known population changes and the assay change (adjusted OR 0.4 (95% CI 0.2 to 2.9), p value=0.21): there was no evidence of a reduction in the overall prevalence of HPV33 or of HPV45. Among women aged 16–18 years with at least one non-vaccine HR-HPV type detected, the prevalence of HPV31/33/45 was 48% lower in the period 4–5 years postvaccination compared to the prevaccination period, with a reduction from 14.9% to 3.7% for HPV31, 9.6% to 7.9% for HPV33, and 11.5% to 6.5% for HPV45 (see online supplementary table S1). In the older age groups, with lower vaccination coverage, there was no evidence of a reduction in these three HPV types between the prevaccination and postvaccination periods.

Non-vaccine HR-HPV types

There was an increase in the prevalence of non-vaccine HR-HPV types between the prevaccination and postvaccination periods at all ages (24.9–33.7%, 26.9–39.6% and 26.4–32.9% for individuals aged 16–18, 19–21 and 22–24 years, respectively). After adjustment for age, venue type, chlamydia positivity and the change in assay, the adjusted ORs comparing the prevaccination and postvaccination prevalence were 1.3 (1.0 to 1.7), 1.5 (1.1 to 2.0) and 1.2 (0.9 to 1.6) for individuals aged 16–18, 19–21 and 22–24 years, respectively (table 3). There was also evidence for increases in the prevalence of the

Table 1 Characteristics of women included in the prevaccination and postvaccination surveys

	Prevaccination (2008) (n=2354)	Postvaccination (2010–2011) (n=3602)	Postvaccination (2012–2013) (n=3719)
Number of samples by laboratory			
North West (Aintree)	472 (20.1%)	170 (4.7%)	350 (9.4%)
Yorkshire and The Humber (Leeds)	–	620 (17.2%)	883 (23.7%)
West Midlands (Stoke)	260 (11.0%)	259 (7.2%)	219 (5.9%)
East of England (Norfolk and Norwich)	759 (32.2%)	222 (6.2%)	123 (3.3%)
East of England (Cambridge)	–	345 (9.6%)	588 (15.8%)
South East (East Kent)	–	563 (15.6%)	935 (25.1%)
South East (Portsmouth)	–	81 (2.2%)	–
South West (Cornwall)	473 (20.1%)	439 (12.2%)	453 (12.2%)
London (University College London)	390 (16.6%)	476 (13.2%)	–
London (Lewisham)	–	427 (11.9%)	168 (4.5%)
Age, years (data completeness)	(100%)	(100%)	(100%)
16–18	1047 (44.5%)	933 (25.9%)	1063 (28.6%)
19–21	804 (34.2%)	1463 (40.6%)	1310 (35.2%)
22–24	503 (21.4%)	1206 (33.5%)	1346 (36.2%)
Ethnicity (data completeness)	(88%)	(76%)	(62%)
White	1924 (92.7%)	2119 (77.1%)	2058 (88.6%)
Black	93 (4.5%)	392 (14.3%)	158 (6.8%)
Asian	25 (1.2%)	75 (2.7%)	46 (2.0%)
Other	34 (1.6%)	144 (5.2%)	46 (2.0%)
Sample collection venue (data completeness)	(100%)	(100%)	(100%)
General practice	608 (25.8%)	1085 (30.1%)	1257 (33.8%)
Family planning (Community Sexual Health Services)	1179 (50.1%)	2429 (67.4%)	2320 (62.4%)
Youth clinic	567 (24.1%)	88 (2.4%)	142 (3.8%)
2+ sexual partners in the previous 12 months (data completeness)	53.6% (81%)	46.6% (45%)	48.6% (31%)
New sexual partner in the previous 3 months (data completeness)	48.1% (81%)	48.1% (47%)	51.3% (32%)
Chlamydia positivity (data completeness)	8.9% (99%)	7.3% (99.8%)	8.5% (100%)
Chlamydia positivity (excluding Leeds and Lewisham) (data completeness)	NA	4.7% (99.8%)	2.7% (100%)
Proportion eligible for HPV vaccination	0.0%	45.6%	61.3%
Estimated vaccination coverage	0.0%	24.3%	35.8%

NA, not applicable.

additional nonavalent HR-HPV types in the age group of 19–21 years. Adjusted ORs were 1.2 (0.9 to 1.7), 1.5 (1.1 to 2.2) and 1.3 (0.9 to 2.0), respectively. This increase in non-vaccine HR-HPV types was only seen between the prevaccination and postvaccination combined periods. Within the postvaccination period, there was no evidence of a change in the prevalence of these HR-HPV types over time (table 2).

The type-specific prevalence of HPV58 was similar in the prevaccination and postvaccination period for all age groups. However, there was an increase in the prevalence of HPV52 even after adjustment (adjusted OR 1.7 (1.0 to 3.2) and 2.4 (1.4 to 4.7), respectively) for individuals aged 16–18 and 19–21 years, and a borderline increase for individuals aged 22–24 years (1.6 (0.9 to 3.6)).

LR HPV6 and/or 11 infection

Similar to the non-vaccine HR types, there was a significant increase in the prevalence of HPV6/11 in the postvaccination period among women aged 16–18 years (5.8% prevaccination vs 8.3% postvaccination; adjusted OR 1.9 (1.1 to 3.4)). There was also a slight increase in the LR types for individuals aged 19–21 years (5.8% vs 7.6%, respectively; adjusted OR 1.4 (0.8 to 2.6)) although after adjustment for age, venue type, chlamydia positivity and the change in assay, this was not significant (p=0.15). There was no evidence of a change in the prevalence of HPV6/11 in the older age group (22–24-years, 4.4% prevaccination vs 4.3% postvaccination; adjusted OR 1.2 (0.6 to 4.1)).

Repeating analyses using PRs instead of ORs (adjusted for all factors except for assay change) gave very similar results for all HPV types (results not shown).

DISCUSSION

This surveillance of young sexually active women undergoing chlamydia screening has demonstrated continuing reductions in the prevalence of the HPV vaccine types following the introduction of a high-coverage national

Table 2 Estimates of prevalence of HPV types by age in prevaccination and postvaccination periods

HPV type	Prevaccination prevalence (%) 2008 (95% CI) n=2354	Postvaccination prevalence (%) 2010–2011 (95% CI) n=3602	Postvaccination prevalence (%) 2012–2013 (95% CI) n=3719	p-value for trend
16–18 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(60.2%)	(73.4%)	
Any high-risk HPV	32.6 (29.7 to 35.4)	37.6 (34.5 to 40.7)	35.4 (32.5 to 38.3)	0.188
Any non-vaccine high-risk HPV	24.9 (22.3 to 27.6)	34.2 (31.1 to 37.2)	33.2 (30.4 to 36.0)	<0.001
Vaccine HPV types				
HPV16 and/or 18	17.6 (15.3 to 19.9)	8.5 (6.7 to 10.3)	4.0 (2.8 to 5.1)	<0.001
HPV16	11.9 (10.0 to 13.9)	6.8 (5.1 to 8.4)	3.0 (2.0 to 4.0)	<0.001
HPV18	7.8 (6.2 to 9.5)	2.8 (1.7 to 3.8)	1.1 (0.5 to 1.8)	<0.001
Nonavalent HPV types*				
HPV31/33/45/52/58	14.5 (12.4 to 16.7)	17.7 (15.2 to 20.1)	14.9 (12.7 to 17.0)	0.835
HPV31/33/45	8.4 (6.7 to 10.1)	6.9 (5.2 to 8.5)	5.8 (4.4 to 7.2)	0.021
HPV31	3.7 (2.6 to 4.9)	0.5 (0.1 to 1.0)	1.2 (0.6 to 1.9)	<0.001
HPV33	2.4 (1.5 to 3.3)	3.5 (2.3 to 4.7)	2.6 (1.7 to 3.6)	0.739
HPV45	2.9 (1.9 to 3.9)	2.9 (1.8 to 4.0)	2.2 (1.3 to 3.0)	0.314
HPV52	4.0 (2.8 to 5.2)	8.6 (6.8 to 10.4)	6.4 (4.9 to 7.9)	0.027
HPV58	3.7 (2.6 to 4.9)	4.0 (2.7 to 5.2)	3.9 (2.7 to 5.0)	0.875
19–21 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(21.4%)	(41.1%)	
Any high-risk HPV	34.3 (31.0 to 37.6)	45.9 (43.4 to 48.5)	44.2 (41.5 to 46.9)	<0.001
Any non-vaccine high-risk HPV	26.9 (23.8 to 29.9)	39.1 (36.6 to 41.6)	40.2 (37.5 to 42.8)	<0.001
Vaccine HPV types				
HPV16 and/or 18	16.9 (14.3 to 19.5)	14.2 (12.4 to 16.0)	8.7 (7.2 to 10.2)	<0.001
HPV16	12.6 (10.3 to 14.9)	11.1 (9.5 to 12.7)	7.5 (6.1 to 8.9)	<0.001
HPV18	6.5 (4.8 to 8.2)	3.8 (2.8 to 4.7)	1.7 (1.0 to 2.4)	<0.001
Nonavalent HPV types*				
HPV31/33/45/52/58	15.2 (12.7 to 17.7)	21.2 (19.1 to 23.3)	20.2 (18.1 to 22.4)	0.015
HPV31/33/45	8.3 (6.4 to 10.2)	8.7 (7.2 to 10.1)	8.8 (7.2 to 10.3)	0.736
HPV31	4.7 (3.3 to 6.2)	2.3 (1.5 to 3.0)	2.7 (1.8 to 3.5)	0.019
HPV33	2.0 (1.0 to 3.0)	2.9 (2.0 to 3.7)	3.4 (2.4 to 4.4)	0.058
HPV45	2.6 (1.5 to 3.7)	3.7 (2.7 to 4.7)	3.2 (2.3 to 4.2)	0.581
HPV52	4.1 (2.7 to 5.5)	10.0 (8.5 to 11.6)	10.3 (8.7 to 12.0)	<0.001
HPV58	5.0 (3.5 to 6.5)	4.6 (3.6 to 5.7)	4.0 (2.9 to 5.0)	0.256
22–24 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(0%)	(1.1%)	
Any high-risk HPV	32.8 (28.7 to 36.9)	40.4 (37.6 to 43.2)	42.4 (39.8 to 45.1)	0.001
Any non-vaccine high-risk HPV	26.4 (22.6 to 30.3)	32.0 (29.4 to 34.6)	33.7 (31.1 to 36.2)	0.007
Vaccine HPV types				
HPV16 and/or 18	15.3 (12.2 to 18.5)	16.5 (14.4 to 18.6)	16.1 (14.2 to 18.1)	0.790
HPV16	10.9 (8.2 to 13.7)	14.7 (12.7 to 16.7)	13.6 (11.8 to 15.4)	0.334
HPV18	5.8 (3.7 to 7.8)	2.7 (1.7 to 3.6)	3.0 (2.1 to 3.9)	0.019
Nonavalent HPV types*				
HPV31/33/45/52/58	16.7 (13.4 to 20.0)	18.4 (16.2 to 20.6)	21.1 (18.9 to 23.3)	0.020
HPV31/33/45	8.9 (6.4 to 11.4)	7.9 (6.4 to 9.4)	10.1 (8.5 to 11.7)	0.196
HPV31	3.2 (1.6 to 4.7)	2.5 (1.6 to 3.4)	2.7 (1.9 to 3.6)	0.770
HPV33	2.6 (1.2 to 4.0)	2.1 (1.3 to 2.9)	3.5 (2.5 to 4.5)	0.111
HPV45	4.2 (2.4 to 5.9)	3.6 (2.6 to 4.7)	4.2 (3.1 to 5.2)	0.837
HPV52	5.2 (3.2 to 7.1)	8.6 (7.0 to 10.2)	9.7 (8.1 to 11.2)	0.005
HPV58	3.0 (1.5 to 4.5)	3.2 (2.2 to 4.1)	3.4 (2.4 to 4.4)	0.605

*Defined as the additional HPV types included in the nonavalent vaccine (31, 33, 45, 52 and 58).
HPV, human papillomavirus.

HPV vaccination programme as well as some evidence of overall reductions in HPV31 (the closely related HPV type with strongest evidence of cross-protection from the bivalent vaccine clinical trials[22]). Encouragingly, these reductions are more marked in the later postvaccination period with higher estimated vaccination coverage. Use of bootstrapping techniques to account for the uncertainty of the specificity and sensitivity estimates from the validation study provided conservative estimates with wider CIs. Once we accounted for this additional

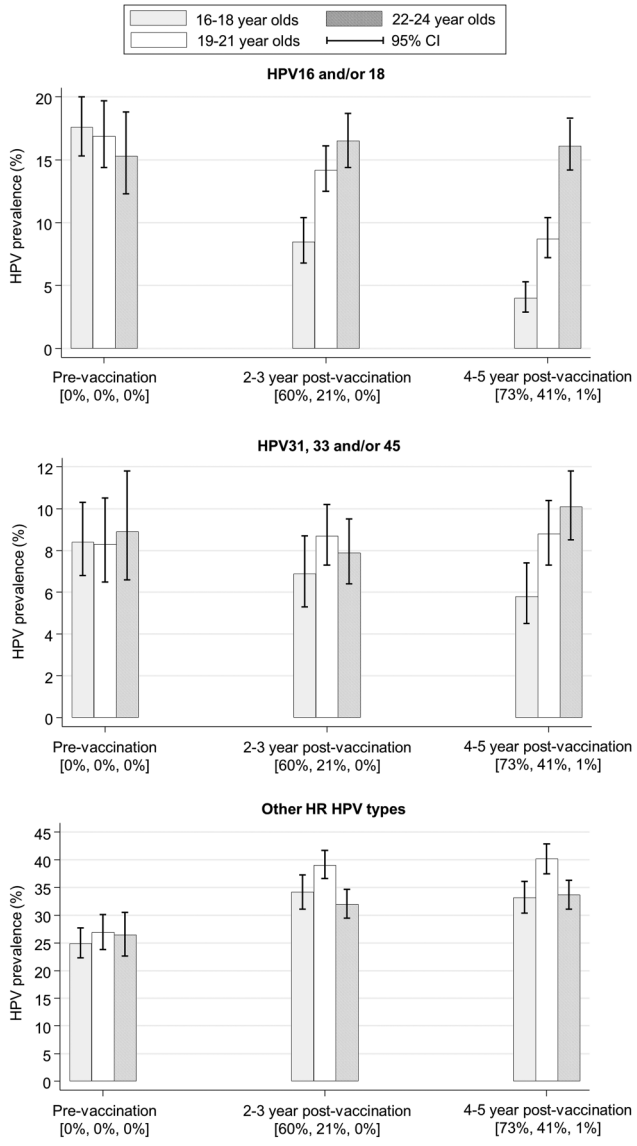

Figure 1 Prevaccination and postvaccination prevalence of human papillomavirus (HPV) types by age. Percentages in square brackets represent estimated three-dose HPV vaccination coverage for individuals aged 16–18, 19–21 and 22–24 years, respectively. HR, high risk.

uncertainty, the reduction in the prevalence of HPV31 postvaccination no longer reached statistical significance.

The percentage reductions between the postvaccination and prevaccination periods among the youngest two age groups were very similar to the estimated vaccine coverage. If all the reduction in prevalence was due to a direct effect of vaccination, this would be consistent with close to 100% vaccine effectiveness. Such high vaccine effectiveness is unlikely given that women included in this surveillance were largely vaccinated as part of the catch-up programme, and almost certainly some of those vaccinated would have had an existing HPV infection. These high reductions could be partly explained by the fact that nationally published data that was used to estimate vaccination coverage is based on reported data on vaccination administration. A recent study of serological markers has suggested that these administration data may be under-reporting HPV vaccinations among women eligible for vaccination as part of the catch-up programme (D Mesher, E Stanford, J White, *et al*. HPV serology testing confirms high HPV immunisation coverage in England. Submitted for publication 2015). This would mean that the vaccination coverage we had estimated for our surveillance population would have been a slight under-estimate. This would be more consistent with the relatively high overall reductions in HPV16/18 we observed although it is most likely that these are due to a combination of both higher vaccination coverage and some herd protection effect.

This surveillance makes use of a large sample of residual specimens taken for chlamydia screening and tested anonymously for HPV-DNA infection. Young women attending for chlamydia screening have higher risks of chlamydia, and therefore, probably for HPV infection, than the general population. The reductions in the HPV vaccine types (HPV16/18) observed here, therefore, reassures that benefits of HPV vaccination have not been inequitably biased to lower risk individuals.

The observation that the reductions in HPV16/18 were only seen in the age groups eligible for national HPV vaccination, and reduced further in the later postvaccination period (ie, were proportionate to estimated vaccination coverage), strongly suggests that the changes seen are attributable to vaccination.

If increases in the other HR-HPV types were restricted to the younger age groups, or were greater in the later postvaccination period with higher vaccination coverage, then this could raise suspicion of potential type replacement. However, the increases seen in the non-vaccine HPV types were seen in all age groups, including the older unvaccinated women, which suggest that these increases are unlikely to be due to type replacement, and are more likely a result of limitations in our study. First, comparison of HPV prevalence between the prevaccination and postvaccination periods were adjusted for age, venue type and chlamydia positivity (as a marker of sexual behaviour). However, other changes in the population characteristics (or sexual behaviour not captured by chlamydia positivity) may have resulted in a change in prevalence of the non-vaccine HR-HPV types. If women in the postvaccination period were at a higher risk of HPV infection then this could have underestimated the potential effect of HPV vaccination on the HPV vaccine types. Analyses restricted to women with at least one HR-HPV type show larger declines for HPV31 and evidence of a reduction in HPV45 which would support this hypothesis. Furthermore, these analyses restricted to HR-HPV-positive specimens show little difference in relative prevalence of HPV52 or 58, which strengthens our conclusion that these increases are probably not due to type replacement. Second, there

Table 3 Prevalence and OR of HPV infection in the postvaccination period compared to prevaccination, by age group

	Prevaccination: n (%)	Postvaccination: n (%)	OR (95% CI)	Adjusted OR* (95% CI)
16–18 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(67.2%)		
HPV16/18 with or without other HR types	184 (17.6%)	121 (6.1%)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)
HPV16/18 alone	80 (7.6%)	55 (2.8%)	0.3 (0.2 to 0.5)	0.5 (0.3 to 1.3)
Non-vaccine HR type(s) with or without HPV16/18	261 (24.9%)	672 (33.7%)	1.5 (1.3 to 1.8)	1.3 (1.0 to 1.7)
HPV31/33/45	88 (8.4%)	126 (6.3%)	0.7 (0.6 to 1.0)	0.9 (0.5 to 1.5)
HPV31/33/45/52/58	152 (14.5%)	323 (16.2%)	1.1 (0.9 to 1.4)	1.2 (0.9 to 1.7)
19–21 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(30.7%)		
HPV16/18 with or without other HR types	136 (16.9%)	322 (11.6%)	0.6 (0.5 to 0.8)	0.6 (0.5 to 0.9)
HPV16/18 alone	60 (7.5%)	153 (5.5%)	0.7 (0.5 to 1.0)	1.2 (0.6 to 4.5)
Non-vaccine HR type(s) with or without HPV16/18	216 (26.9%)	1098 (39.6%)	1.8 (1.5 to 2.1)	1.5 (1.1 to 2.0)
HPV31/33/45	67 (8.3%)	242 (8.7%)	1.1 (0.8 to 1.4)	1.3 (0.8 to 2.6)
HPV31/33/45/52/58	122 (15.2%)	575 (20.7%)	1.5 (1.2 to 1.8)	1.5 (1.1 to 2.2)
22–24 years				
(Estimated HPV16/18 vaccination coverage)	(0%)	(0.6%)		
HPV16/18 with or without other HR types	77 (15.3%)	416 (16.3%)	1.1 (0.8 to 1.4)	1.1 (0.8 to 1.7)
HPV16/18 alone	32 (6.4%)	219 (8.6%)	1.4 (0.9 to 2.0)	2.5 (1.2 to 329.2)
Non-vaccine HR type(s) with or without HPV16/18	133 (26.4%)	839 (32.9%)	1.4 (1.1 to 1.7)	1.2 (0.9 to 1.6)
HPV31/33/45	45 (8.9%)	231 (9.1%)	1.0 (0.7 to 1.4)	1.2 (0.7 to 2.5)
HPV31/33/45/52/58	84 (16.7%)	506 (19.8%)	1.2 (1.0 to 1.6)	1.3 (0.9 to 2.0)

*Adjusted for age, venue type, chlamydia positivity and change in HPV assay between prevaccination and postvaccination period.
HPV, human papillomavirus.

was a change in the assay used between the postvaccination and prevaccination periods, but no change in the assay used throughout the postvaccination period; hence, continued reductions in the vaccine HPV types within the postvaccination period cannot be affected by this. However, it was necessary to adjust ORs comparing the prevaccination and postvaccination periods for the different assays used. Finally, broad-spectrum assays, such as those used in our study, can lack sensitivity to detect individual HPV types at low copy number in the presence of other HPV types. Therefore, the decrease in multiple HPV infections due to the reduction in HPV16 and 18 following vaccination could lead to an apparent, artificial increase in the prevalence of certain non-vaccine HPV types (ie, unmasking). Given that the increases in certain HPV types were apparent between the prevaccination and postvaccination periods, but remained relatively stable within the postvaccination period, this suggests that unmasking is not playing a huge role in these increases. However, while adjustment was made for the change in assay between the two periods, to what extent increases in non-vaccine types are due to temporal changes, changes in the population undergoing chlamydia screening, or changes in the detection accuracy of assays, is still somewhat unclear.

In England, the quadrivalent vaccine was introduced to the national HPV immunisation programme from 2012 as part of routine vaccination of 12-year-old girls. At the time this surveillance was conducted, the oldest women vaccinated with the quadrivalent vaccine as part of the national programme would have been 14 years old, hence, too young to be included in this surveillance (conducted among individual aged 16–24 years). Therefore, all women included in this surveillance who were vaccinated as part of the national immunisation programme would have received the bivalent HPV vaccine. We were unable to link these specimens to individual HPV vaccination status, and coverage estimates were derived from published data. This meant that we considered population-level impact of HPV vaccination rather than direct calculation of vaccine effectiveness. Our findings of reductions in the prevalence of the HPV vaccine types are consistent with surveillance conducted in other countries, although changes in the prevalence of non-vaccine HR-HPV types varied.[27] Tabrizi *et al*[14] showed a 77% reduction in the prevalence of HPV vaccine types among young women attending for a Pap test in Australia. In the USA, reductions in the prevalence of HPV vaccine types were 56% in individuals aged 14–19 years, despite a low self-reported vaccination coverage (34% with one or more doses). [17] In Sweden, surveillance also among women attending for chlamydia screening found a reduction of 42% in HPV16 and 46% in HPV18 among females aged 13–22 years, and also a slight increase in HPV52 and 56.[19] In Scotland, where cervical screening is offered from age 20 years, a 54% reduction in the vaccine types has been shown in individuals aged 20 years, as well as a 48% reduction in the cross-protection types HPV31, 33 and 45.[18]

We have analysed HPV type-specific prevalence among almost 10,000 women over a period of 5 years. These data provide clear evidence of a reduction in the HPV vaccine types, and a suggestion of a reduction in HPV31, a closely related HPV type, since the introduction of the HPV immunisation programme in England. This will both inform future decisions regarding HPV vaccination in England and be of interest to other countries seeking to monitor the impact of HPV vaccination.

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Contributors This surveillance was initiated and designed by KS. DM and KS were responsible for the sample collection and data management. SB and KP performed the HPV testing. DM conducted the statistical analysis. SLT contributed to the data analysis and interpretation. DM, KS and SLT wrote the first draft of the manuscript. All authors contributed to and approved the final draft.

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REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
2. IARC Working Group. *IARC monographs on the evaluation of carcinogenic risks to humans*. Lyon, France: World Health Organisation International Agency for Research on Cancer, 2012.
3. Li N, Franceschi S, Howell-Jones R, *et al*. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. *Int J Cancer* 2011;128:927–35.
4. Mesher D, Cuschieri K, Hibbitts S, *et al*. Type-specific HPV prevalence in invasive cervical cancer in the UK prior to national HPV immunisation programme: baseline for monitoring the effects of immunisation. *J Clin Pathol* 2015;68:135–40.
5. Bosch FX, Broker TR, Forman D, *et al*. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine* 2013; 31(Suppl 8):I1–31.
6. Cervical Cancer Action. Global Progress in HPV Vaccination. http://www.cervicalcanceraction.org/comments/comments3.php (accessed Nov 2014).
7. Department of Health, Health Protection Agency. Annual HPV vaccine uptake in England: 2010/11. http://webarchive.nationalarchives.gov.uk/20130107105354/https://www.wp.dh.gov.uk/immunisation/files/2012/03/120319_HPV_UptakeReport2010–11-revised_acc.pdf (accessed Apr 2015).
8. Department of Health, Health Protection Agency. Annual HPV vaccine uptake in England: 2011/12. http://webarchive.nationalarchives.gov.uk/20130123170526/http://immunisation.dh.gov.uk/ann-hpv-vac-cover-england-201112/ (accessed Apr 2015).
9. Public Health England. Annual HPV vaccine coverage in England: 2012/13. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/266190/HPV_AnnualDataTable2012_13_SHA_acc2.pdf (accessed Apr 2015).
10. Markowitz LE, Tsu V, Deeks SL, *et al*. Human papillomavirus vaccine introduction—the first five years. *Vaccine* 2012;30(Suppl 5):F139–48.
11. Public Health England. Human Papillomavirus (HPV) Vaccine Coverage in England, 2008/09 to 2013/14: A review of the full six years of the three-dose schedule. https://www gov uk/government/uploads/system/uploads/attachment_data/file/412264/HPV_Vaccine_Coverage_in_England_200809_to_201314 pdf 2015 (accessed Oct 2015).
12. Rondy M, van Lier A, van de Kassteele J, *et al*. Determinants for HPV vaccine uptake in the Netherlands: a multilevel study. *Vaccine* 2010;28:2070–5.
13. Mesher D, Soldan K, Howell-Jones R, *et al*. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. *Vaccine* 2013;32:26–32.
14. Tabrizi SN, Brotherton JM, Kaldor JM, *et al*. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis* 2012;206:1645–51.
15. Cummings T, Zimet GD, Brown D, *et al*. Reduction of HPV infections through vaccination among at-risk urban adolescents. *Vaccine* 2012;30:5496–9.
16. Kahn JA, Brown DR, Ding L, *et al*. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. *Pediatrics* 2012;130:e249–56.
17. Markowitz LE, Hariri S, Lin C, *et al*. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. *J Infect Dis* 2013;208:385–93.
18. Kavanagh K, Pollock KG, Potts A, *et al*. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. *Br J Cancer* 2014;110:2804–11.
19. Soderlund-Strand A, Uhnoo I, Dillner J. Change in population prevalences of human papillomavirus after initiation of vaccination: the high-throughput HPV monitoring study. *Cancer Epidemiol Biomarkers Prev* 2014;23:2757–64.
20. Brown DR, Kjaer SK, Sigurdsson K, *et al*. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years. *J Infect Dis* 2009;199:926–35.
21. Malagon T, Drolet M, Boily MC, *et al*. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:781–9.
22. Wheeler CM, Castellsague X, Garland SM, *et al*. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 2012;13:100–10.
23. Howell-Jones R, de Silva N, Akpan M, *et al*. Prevalence of human papillomavirus (HPV) infections in sexually active adolescents and young women in England, prior to widespread HPV immunisation. *Vaccine* 2012;30:3867–75.
24. Bissett SL, Howell-Jones R, Swift C, *et al*. Human papillomavirus genotype detection and viral load in paired genital and urine samples from both females and males. *J Med Virol* 2011;83:1744–51.
25. Joura EA, Giuliano AR, Iversen OE, *et al*. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015;372:711–23.
26. Department of Health, Health Protection Agency. Annual HPV vaccine coverage in England in 2009/2010. https://www.gov.uk/government/publications/annual-hpv-vaccine-coverage-in-england-in-2009–2010 (access Apr 2015).
27. Drolet M, Benard E, Boily MC, *et al*. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015;15:565–80.

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