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Factors associated with failed 'test of cure' in the NHS Cervical Screening Programme: A retrospective cohort study

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HIGHLIGHTS

- Patients referred with a singular HPV genotype were more likely to pass test of cure than those with multiple HPV genotypes.
- Failed test of cure was associated with HPV Other (HPV O) and age ≥51 years at referral.
- HPV genotype should be reported as standard on all cervical screening samples.
- The term HPV O should not be used. Instead the actual HPV genotype should be reported.

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ABSTRACT

Objective. To determine predictive factors associated with failed 'test of cure' (TOC) in the NHS Cervical Screening Programme (NHSCSP).

Methods. Retrospective cohort study of all patients treated by large loop excision of transformation zone (LLETZ) between 1st April 2014 and 1st April 2019. Those with no documented HPV genotype on referral, no TOC outcome, those having a hysterectomy, chemotherapy and/or radiotherapy were excluded from final analysis.

Results. Patients referred with a singular HPV genotype of HPV 16, HPV 18, or HPV Other types (HPV O) were significantly more likely to pass TOC than those referred with multiple HPV genotypes ($p < 0.0001$). Those with HPV genotypes including HPV O were significantly more likely to fail TOC as compared to those with genotypes of solely HPV 16 and/or 18 ($p < 0.0001$).
Patients aged ≥51 years were significantly more likely to fail TOC when compared to all other age groups ($p < 0.0001$).

Conclusion. Age >51 yrs. and infection with multiple hr-HPV types were predictors of post treatment hr-HPV persistence. Knowledge of HPV genotype both at referral, and following treatment, could allow a more individualised, and patient-centred, approach to both the management and follow up of CIN. HPV genotype should be reported as standard on all cervical screening sample results. The term HPV O should not be utilised and instead actual HPV genotype should be reported. This would enable us to optimise not only future research but would also allow future monitoring of the efficacy of vaccination programmes.

1. Introduction

Human papillomavirus (HPV) is accepted as responsible for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer [1–4]. High-risk HPV (hr-HPV) screening is also a better predictor of disease than cytology alone [2,5]. The presence of hr-HPV following treatment for CIN, or cervical glandular intraepithelial neoplasia (CGIN), is a risk factor for disease persistence, recurrence, and new HPV infection. It is also considered a potential cause for future disease [6,7].

Within the NHS Cervical Screening Programme (NHSCSP) a 'test of cure' (TOC) sample following treatment for CIN/CGIN is therefore

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recommended at six-months post treatment to determine the presence of hr-HPV and inform the timescale for further cervical screening [8]. Samples are tested for hr-HPV; if hr-HPV is not detected patients return to routine recall at three years; if hr-HPV is detected, reflex cytology is performed as recommended by the NHSCSP, and patients are referred-back to colposcopy irrespective of the cytology result. These cases are regarded as those failing TOC. European, American, and Australian guidelines also recommend the use of hr-HPV as a TOC yet there is no consensus practice regarding screening intervals, and duration of follow up. As is also seen within England, there is heterogeneity with respect to standardised reporting of HPV genotype on cervical sample reports [9–11].

Failed TOC referrals (i.e. those with hr-HPV detected post-treatment) have a significant impact upon colposcopy services and patients, resulting in increased workload for colposcopy units and increased anxiety and potential interventions for the patients. Whilst persistence of any hr-HPV infection results in TOC failure, the influence of the different hr-HPV genotypes on treatment outcomes is poorly understood. This study aims to determine predictive factors associated with failed TOC and add to the body of evidence in favour of type-specific HPV reporting.

2. Methodology

This study is a retrospective cohort study with interval analysis between 1st April 2014 and 1st April 2019 performed at the Jessop Wing Colposcopy Unit, Sheffield, UK. The colposcopy database and Royal Hallamshire Hospital pathology database were searched for all patients undergoing treatment by large loop excision of the transformation zone (LLETZ) (a common way to remove abnormal cells from the cervix). The Trust based integrated clinical environment (ICE™) system (established web-based requesting and reporting service) and Open Exeter (web-enabled database) were searched for subsequent HPV and cytology results at six to twelve months (to allow time for TOC attendance) post treatment. If no sampling had occurred by twelve months, the next available screening result was identified and documented.

Data including patient age at appointment, tobacco smoking status, referral cytology, referral HPV genotype, treatment method ('see & treat' vs. 'select & treat' vs. repeat LLETZ / local vs. general anaesthetic), LLETZ excision status (complete vs. incomplete margins of excision), depth of LLETZ specimen, and LLETZ histology results were analysed against TOC outcomes (hr-HPV not detected, hr-HPV detected cytology negative / hr-HPV detected cytology abnormal). Those with no documented HPV genotype on referral (HPV genotype omitted from referral cytology report)or no TOC outcome were excluded from further analysis as were those having a hysterectomy, or chemotherapy and radiotherapy for a diagnosis of cervical cancer.

All cytology specimens were processed by means of *SurePath*® (liquid-based cytology), all HPV testing was performed using Cobas 4800® reporting HPV 16, HPV 18, and HPV Other types (HPV O) (including HPV 31,33,35,39,45,51,52,56,58,59,66,68). Cervical biopsies and LLETZ specimens were reviewed by specialised gynaecological histopathologists.

Demographic and baseline statistical analyses were performed using Microsoft Excel and 'Graphpad' software. Chi squared test was used to determine statistical significance. As this study was performed in the context of a service review ethical approval was not required.

3. Results

Between 1st April 2014 and 31st March 2019, 2605 patients underwent a LLETZ procedure. Median age at LLETZ was 30 years (range 22–77 yrs); 31% ($n = 799$) were registered as tobacco smokers at the time of treatment. LLETZ were conducted on patients referred with high-grade cytological abnormality (moderate dyskaryosis or worse) ($n = 1801$, 69%); low-grade cytological abnormality ($n = 474$, 18%) (borderline & mild dyskaryosis); and negative cytology persistent hr-HPV detected ($n = 174$, 7%). Glandular changes in endocervical cells accounted for 105 referrals (4%), and 51 (2%) were referred with clinical indications (e.g. post-coital bleeding, abnormal cervix).

Almost all LLETZ procedures were performed under local anaesthetic ($n = 2552$; 98%). Most were performed as a 'see and treat' procedure (treated at initial colposcopy visit when a high-grade lesion was clinically suspected by the attending clinician) ($n = 1476$; 57%), 1092 (42%) were performed following biopsy proven disease (select & treat), and a small number were repeat LLETZ procedures ($n = 37$; 1%). In 2425 (93%) cases the LLETZ sample was removed as a single specimen.

Histology revealed high-grade CIN in 80% of cases ($n = 2086$); CGIN in 4% ($n = 100$); invasive disease in 3% ($n = 70$). Low-grade CIN was detected in 4% ($n = 110$); and no evidence of intraepithelial neoplasia (negative LLETZ) was found in 9% ($n = 239$) (Table 1). Median depth of LLETZ was 10 mm with the majority showing complete margins of excision ($n = 1960$; 75%).

Patients referred with high-grade cytology were significantly more likely to have high-grade changes at histology than any other histological finding ($p < 0.0001$). Those referred with clinical indications, were significantly more likely to have high-grade changes on histology than low-grade or negative findings ($p = 0.018$).

Excluding those with unknown HPV genotype, and those referred for clinical indications, data for 2212 cases were analysed by HPV genotype at referral. The majority referred with negative cytology hr-HPV detected had HPV 16 ($n = 65$; 37.3%) or HPV O ($n = 60$; 34.5%). For those referred with low-grade cytology, the predominant HPV genotypes were HPV O ($n = 207$; 43.7%) and HPV 16 ($n = 90$; 19%). Within the high-grade referral cytology group HPV O ($n = 622$; 34.5%) and HPV 16 ($n = 453$; 25.2%) were most common. One third of patients referred with glandular changes at cytology were found to have HPV 18 ($n = 38$; 36.3%) and one quarter were found to have HPV 16 ($n = 26$; 24.8%).

Excluding those diagnosed with ungraded CIN or stratified mucin-producing intraepithelial lesion (SMILE), data for 2236 cases were analysed by HPV referral genotype and LLETZ histology. Those with CGIN were significantly more likely to have HPV 18 at referral than any other HPV genotype ($p < 0.0001$). Patients with invasive disease were significantly more likely to have HPV 16 at referral when compared to all other HPV genotypes ($p = 0.0086$). Patients with no CIN were significantly more likely to have HPV O ($p = 0.0313$). For those patients with CIN1, HPV O was the most common genotype ($n = 46$; 46.5%) followed by HPV 16 ($n = 25$; 25.3%). For patients with high-grade histological changes (CIN2/3) HPV O was the most common referral genotype ($n = 741$; 41.6%), followed by HPV 16 ($n = 519$; 29.2%) (Table 2).

3.1. Test of cure (TOC) outcomes by referral cytology

Those with no TOC result ($n = 214$) were excluded from the final analysis. Those referred with glandular cytological abnormalities were significantly less likely to attend for TOC, despite standard clinician recommendation, as compared to those referred with other cervical screening abnormalities ($p = 0.0103$). Of the 2391 remaining cases 564 (23.6%) failed their TOC sample (Table 3).

Patients referred with glandular changes on cytology, attending for TOC, were significantly less likely to fail TOC compared to those referred with other cervical screening abnormalities ($p = 0.0217$).

3.2. Test of cure (TOC) outcomes by referral HPV genotype

Excluding those with no TOC result ($n = 214$), and those with no HPV genotype available ($n = 322$), a total of 2069 cases were included. Patients referred with multiple HPV genotypes of HPV 16, 18 & O, and 16 & O had the highest rates of failed TOC at 45.8% and 41.6% respectively. Those referred with HPV 18 had the lowest rate of failed TOC (15.3%).

Table 1
Demographic Data: LLETZ performed between 1st April 2014 and 31st March 2019 at Jessop Wing Colposcopy Unit, Sheffield, UK.

	Year					Total	Percent
	1st April 2014 to 31st March 2015	1st April 2015 to 31st March 2016	1st April 2016 to 31st March 2017	1st April 2017 to 31st March 2018	1st April 2018 to 31st March 2019		
n	611	683	453	422	436	2605	
Median age (yrs)	29	30	31	31	31	30	
(range)	(23–67)	(22–77)	(24–65)	(24–73)	(24–74)	(22–77)	
Referral Cytology							
Negative; hrHPV detected	16	33	27	60	38	**174**	**7%**
Low-grade	98	118	89	72	97	**474**	**18%**
High-grade	456	489	304	271	281	**1801**	**69%**
Glandular	31	30	26	12	6	**105**	**4%**
Clinical Indication Referral	10	13	7	7	14	**51**	**2%**
Anaesthetic type							
Local	594	674	445	413	426	**2552**	**98%**
General	17	9	8	9	10	**53**	**2%**
Treatment Method							
See & Treat LLETZ	335	353	252	240	250	**1430**	**55%**
Select & Treat LLETZ	272	330	201	179	173	**1155**	**44%**
Repeat LLETZ	4	0	0	3	13	**20**	**1%**
Specimen Removed as Single Sample							
Yes	560	629	430	395	411	**2425**	**93%**
No	51	54	23	27	25	**180**	**7%**
Excision Status							
Complete	432	550	353	311	314	**1960**	**75%**
Incomplete	179	133	100	111	122	**645**	**25%**
Median depth of excision (mm)	8.5	9	10	10	10	**10**	
LLETZ Histology Result							
No CIN	36	55	36	31	44	**202**	**8%**
CIN1	16	24	28	10	29	**107**	**4%**
CIN2	90	126	101	91	71	**479**	**18%**
CIN3	425	441	247	261	259	**1633**	**63%**
CGIN	30	28	24	13	19	**114**	**4%**
Invasive Disease	14	9	17	16	14	**70**	**3%**

CIN – cervical intraepithelial neoplasia; CGIN – cervical glandular intraepithelial neoplasia; hrHPV – high-risk human papillomavirus, LLETZ – large loop excision of the transformation zone.

Patients referred with a singular HPV genotype of HPV 16, HPV 18, or HPV O were significantly more likely to pass TOC than those referred with multiple HPV genotypes ($p < 0.0001$). Likewise, patients with HPV genotypes including HPV O were significantly more likely to fail TOC as compared to those with genotypes of HPV 16 and/or 18 ($p < 0.0001$).

3.3. Test of cure (TOC) outcomes by age

When considering TOC outcomes by age, failure rates remained stable below the age of 51 years. The highest failure rates were detected in the >65 years age group (57%).

Patients aged ≥51 years were significantly more likely to fail TOC when compared to all other age groups ($p < 0.0001$). Whilst a trend

Table 2
Histology outcome at LLETZ by HPV referral genotype.

		Histology outcome at LLETZ				
HPV Genotype	n	No CIN	Low-grade CIN	High-grade CIN	CGIN	Invasive Disease
16	644	58 (9%)	25 (3.9%)	519 (80.6%)	15 (2.3%)	27 (4.2%)
18	133	17 (12.8%)	7 (5.3%)	63 (47.3%)	37 (27.8%)	9 (6.8%)
16 &18	33	1 (3%)	0	27 (81.9%)	4 (12.1%)	1 (3%)
16 & other	420	22 (5.2%)	11 (2.6%)	364 (86.7%)	11 (2.6%)	12 (2.9%)
18 & other	75	9 (12%)	9 (12%)	43 (57.4%)	12 (16%)	2 (2.6%)
16,18 & other	27	2 (7.4%)	1 (3.7%)	23 (85.2%)	1 (3.7%)	0
Other	904	99 (11%)	46 (5.1%)	741 (81.9%)	9 (1%)	9 (1%)
Total	**2236**	208 (9.3%)	99 (4.4%)	1780 (79.6%)	89 (4%)	60 (2.7%)

CIN – cervical intraepithelial neoplasia; CGIN – cervical glandular intraepithelial neoplasia; HPV – human papillomavirus, LLETZ – large loop excision of the transformation zone.

Table 3
Test of Cure outcomes by referral cytology, HPV genotype & age.

		n	HPV Negative	Failed TOC	No TOC Performed
Test of Cure outcomes by referral cytology					
Referral Cytology	Negative	**174**	126 (72%)	38 (22%)	10 (6%)
	Low-grade	**474**	333 (70%)	107 (23%)	34 (7%)
	High-grade	**1801**	1261 (70%)	393 (22%)	147 (8%)
	Glandular	**105**	77 (73.3%)	12 (11.4%)	16 (15.3%)
	Clinical Indication	**51**	30 (58.8%)	14 (27.5%)	7 (13.7%)
	Total	**2605**	**1827 (70%)**	**564 (22%)**	**214 (8%)**
Test of Cure outcomes by referral HPV genotype					
HPV Genotype	16	**592**	487 (82.3%)	105 (17.7%)	
	18	**124**	105 (84.7%)	19 (15.3%)	
	16 & 18	**30**	20 (66.7%)	10 (33.3%)	
	16 & other	**382**	223 (58.4%)	159 (41.6%)	
	16,18 & other	**24**	13 (54.2%)	11 (45.8%)	
	18 & other	**73**	58 (79.5%)	15 (20.5%)	
	Other	**844**	669 (79.3%)	175 (20.7%)	
	Total	**2069**	**1575 (76.1%)**	**494 (23.9%)**	
Test of Cure outcomes by Age					
Age (years)	≤25	451	347 (77%)	104 (23%)	
	26–30	771	600 (78%)	171 (22%)	
	31–35	440	344 (78%)	96 (22%)	
	36–40	248	202 (81.5%)	46 (18.5%)	
	41–50	318	237 (74.5%)	81 (25.5%)	
	36–50	**566**	**439 (78%)**	**127 (22%)**	
	51–65	156	94 (60%)	62 (40%)	
	>65	7	3 (43%)	4 (57%)	
	Total	**2391**	**1827 (76.5%)**	**564 (23.5%)**	
Test of Cure outcomes by final histology result					
No CIN		**239**	168 (70%)	52 (22%)	19 (8%)
Low-grade CIN		**110**	67 (61%)	33 (30%)	10 (9%)
High-grade CIN		**2086**	1468 (70%)	454 (22%)	164 (8%)
CGIN		**100**	76 (76%)	8 (8%)	16 (16%)
Invasive disease		**70**	30 (43%)	6 (9%)	34 (48%)
Total		**2605**	**1809 (70%)**	**553 (21%)**	**243 (9%)**

CIN – cervical intraepithelial neoplasia; CGIN – cervical glandular intraepithelial neoplasia; HPV – human papillomavirus; TOC – test of cure.

was observed with those >65 years of age having higher rates of failed TOC as compared to those aged 51–65 years, statistical significance was not achieved. This may reflect the low numbers of patients in the >65 years category ($n = 7$) (Table 3).

3.4. TOC outcomes by histology result

Patients with low-grade CIN had the highest rate of failed TOC (30%). Those with no CIN, and those with high-grade CIN had similar proportions of failed TOC (22%). Those with invasive disease had lower rates of failed TOC (9%), this could perhaps be accounted for by the large number having no TOC performed due to ongoing treatment by hysterectomy and/or chemo-radiotherapy for their invasive disease. Patients with CGIN were less likely to fail their TOC (8%). No statistically significant differences were identified between final histology and failed TOC.

3.5. TOC outcomes by histology and depth / completeness of LLETZ excision

Two of 33 patients (6%) diagnosed with early-stage cervical cancer failed TOC. In those diagnosed with CIN (1849), 130 (7%) failed TOC with just over one half having an excision depth ≥ 10 mm (53%, $n = 69$); one third (35%, $n = 46$) with an excision depth of 7-9 mm and the remaining 12% ($n = 15$) an excision depth < 7 mm. Two thirds ($n = 86$) had complete excision margins reported on histology. In those diagnosed with CGIN ($n = 79$), only three (4%) failed TOC. Of these, one had an excision depth of 7-9 mm and two ≥10 mm. Two of these women had complete excision margins; one incomplete.

Neither depth of excision, nor completeness of margins of excision, correlated with hr-HPV status at TOC.

Tobacco smoking status was not found to be associated with failed test of cure with 29% of those passing TOC versus 33% of those failing TOC registered as smokers ($p = 0.1161$).

4. Discussion

HPV 16 is recognised as the most oncogenic genotype [3,6,8,12–17]. Our study supports this finding with those diagnosed with invasive disease significantly more likely to have HPV 16 than any other hr-HPV genotype. We also found, in agreement with prior study findings, with similar patient demographics [9,10,14,17], that those referred with glandular changes in endocervical cells, and those diagnosed with CGIN, were significantly more likely to have HPV 18 than any other hr-HPV genotype. Our failed TOC rates were similar with those of prior UK published data [18], yet lower than those reported by other studies [13,19,20] making our study findings of over 2000 patients comparable to data from prior publications.

The aim of this study was to identify factors associated with failed TOC. Whilst patients referred with glandular changes in endocervical cells were significantly less likely to attend for TOC, those that did attend were significantly less likely to fail TOC as compared to those referred with other cervical screening abnormalities. The majority, referred with glandular changes, undergo a 'see & treat' procedure within our unit in view of the significant risk of underlying CGIN, and will more frequently have a larger sized LLETZ when CGIN is detected to ensure clearance of the endocervical margin. It is possible, that these patients are less likely to fail TOC in view of more aggressive treatments and increased depths of excision. However, falling in line with prior study findings [11], this study found that neither depth of excision, nor completeness of margins of excision, correlated with hr-HPV status at TOC, and no statistically significant differences were identified between final histology and failed TOC. It should therefore be questioned as to whether the reason these patients are less likely to fail TOC is related to the higher proportion infected with HPV 18 and the ensuing effect of treatment upon clearance of this HPV genotype. Others have however reported that persistence rates of HPV 16 following treatment were lower than that of other hr-HPV types [21].

The presence of hr-HPV following treatment for CIN, or CGIN, is a known risk factor for disease persistence or recurrence [14], with those testing hr-HPV negative having a 6.5% risk of residual or recurrent disease, and those testing positive a >60% risk [22]. This study found that infection with multiple hr-HPV genotypes on referral, and patients with HPV genotypes including HPV O, were significantly more likely to fail TOC.

Infection with multiple hr-HPV types has been reported as an independent predictor of residual and recurrent CIN [13,23]; and infection with multiple hr-HPV types, before treatment, as increasing the risk of persistent hr-HPV. Infection with multiple HPV types is reported in 20 to 40% of HPV-positive patients [23], with specific HPV genotypes having different natural histories, and different oncogenic potential [21]. Little is understood however regarding the potential interaction between multiple HPV types in the induction, progression, and persistence of cervical lesions, the effect on viral load, or the potential for relative viral latency in some hr-HPV types, when multiple HPV infections are identified [23]. It is important to recognize therefore that oncogenic potential does not necessarily equate to persistent infection, and indeed it may be the case that mixed HPV genotypes present more of a challenge to the immune system. What is clear however is that in terms of HPV persistence, detailed analysis of specific HPV genotypes may help expand our understanding of the nature of HPV infections and their impact on cervical disease [21].

Considering the differences in outcomes of TOC with varying HPV genotypes, knowledge of HPV genotype both at referral, and following treatment, could allow a more individualised, and patient centred, approach to both the management and follow up of CIN. This is an opinion supported by numerous prior studies reported in the literature

[13,24–26]. There is therefore a logical argument that actual HPV genotype, instead of HPV O should be reported as standard on all cervical screening sample results. This would enable us to optimise not only future research but could also enable future monitoring of the efficacy of the NHS HPV vaccination programme.

Age is reported as a risk factor for the persistence of hr-HPV following treatment for CIN [19,27–29]. Our study supports this finding with patients ≥51 years more likely to test positive for hr-HPV following treatment. Post-menopausal status has also been identified as an independent predictor of residual/recurrent CIN [13]. It has been suggested that post treatment persistence of hr-HPV in older, postmenopausal patients is related to the fact that the squamo-columnar junction is deeper within the cervical canal than in pre-menopausal patients and, due to limited resection depths, this could consequently interfere with complete hr-HPV eradication or CIN removal [13]. We disagree with this however as in our study neither depth of excision, nor completeness of margins of excision, correlated with hr-HPV status at TOC. We would consider post treatment persistence of hr-HPV in older patients to be more likely related to a reduced immune response associated with aging. The risk of oncogenic HPV reactivation may increase after the age of 50 years and this may contribute to the large proportion of HPV detection at older ages, compared with the proportion resulting from new HPV infections [30]. The phenomenon, known as immunosenescence, which involves a reduction in many aspects of immune system function, naturally occurs during the aging process. Immunosenescence leading to reactivation of HPV has been hypothesized as an explanation for higher prevalence proportions amongst older patients [31]. Further research however is needed to help better understand the natural history of HPV infection in the older population and to understand the importance of HPV persistence and reactivation.

Colposcopy, at The Jessop Wing Unit, is practiced with adherence to current national guidelines and, this study includes a large number of patients for whom HPV genotype was available. Findings from this study are therefore applicable to England and, most of the UK. Limitations of this study however are the low number of glandular referrals and CGIN diagnoses and the proportion of TOC samples taken outside of the 6 month post treatment window which increases the likelihood of repeat infection. Our study is also limited by the fact that whilst HPV16 and HPV 18 are reported as individual genotypes in England, all other genotypes are categorised as HPV O thus limiting our analysis on which hr-HPV genotypes truly persist following treatment. Furthermore, studies in England are limited as HPV viral load is not reported as standard and pre-treatment HPV viral load has been reported as an independent predictor of persistence [13,32], with the risk of residual/recurrent CIN significantly greater in patients with a higher HPV load at baseline [13,33]. It is possible that infection with multiple HPV genotypes may increase viral load. Given these limitations, multivariate analyses were not carried out on this data.

Moving forward however, national pooling of data would provide larger numbers to analyse, offer the potential to answer the question of why women fail TOC and, also enable us to further analyse data regarding negative LLETZ findings with the aim of reducing unnecessary procedures for these women.

5. Conclusion

Patients with multiple hr-HPV genotypes at presentation have a higher rate of failed TOC than those with a single genotype including HPV 16. Although HPV 16 is known to be the most oncogenic of all high-risk types leading to a higher risk of high-grade CIN and invasive disease, this study found it is only when combined with HPV O genotypes that HPV 16 is more likely to persist following LLETZ leading to failed TOC. We recommend a move away from reporting HPV O to reporting of specific HPV genotypes to allow further research on the interaction between different hr-HPV types to enable clinicians to personalise management and triage follow up for patients with pre-invasive cervical disease. We are aware of the significant cost implications associated with implementing this strategy and complications related to validation by the NHSCSP, however, reporting of specific HPV genotypes would also improve future monitoring of the efficacy of HPV vaccination programmes.

Author contributions

Conceptulization: EL, RL, JP. Data curation: RL, JEP. Methodology: JEP. Formal analysis: EL, VLP, JEP. Validation: KE, RL, MCM, VLP, JEP. Writing - original draft: EL,KE, JEP. Writing- review and editing: MCM, VLP, RL, KE, JEP. Supervision: MCM, JEP.

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Consent statement

As this study was performed in the context of a service review ethical approval was not required.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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