

1 **Reduction in colposcopy workload and associated clinical activity following HPV catch-up vaccination**
2 **programme in Scotland: an ecological study**

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25 Running title

26 Reduced Scottish colposcopy activity after HPV vaccination

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Abstract

Objective: To measure patterns of clinical activity at colposcopy before and after vaccinated women entered the Scottish Cervical Screening Programme (SCSP).

Design: Population-based observational study using nationally collected data.

Setting: Scottish colposcopy clinics.

Sample: All women with a date of birth on or after 1 January 1985 who attended colposcopy in Scotland between 2008-2014.

Methods: Routinely collected data from the Scottish National Colposcopy Clinical Information Audit System (NCCIAS) was extracted, including: referral criteria, referral cervical cytology, colposcopic findings, clinical procedures and histology results. Analysis was restricted to those referred to colposcopy at age 20 or 21 years.

Main outcome measures: Referral criteria, positive predictive value of colposcopy, default rates and rates of cervical biopsies and treatments.

Results: 7372 women referred for colposcopy at age 20/ 21 years were identified. There was a downward trend in the proportion of those referred with abnormal cytology (2008/9: 91.0%, 2013/14: 90.3%, linear trend p value = 0.03). Women were less likely to have diagnostic or therapeutic interventions. The proportion with no biopsy (2008/9: 19.5%, 2013/14: 26.9%, linear trend p value < 0.0001) and no treatment (2008/9: 74.9%, 2013/14: 91.8%, linear trend p value < 0.0001) increased over the period of observation.

Conclusions: A reduction in clinical activity related to abnormal screening referrals is likely to be associated with the HPV catch-up immunisation programme. Referral criteria and service provision of colposcopy needs

56 to be planned carefully taking account of the increasing number of HPV- immunised women that will be
57 entering cervical screening programmes worldwide.

58

59 Word count 249

60 **Key words:** HPV, HPV vaccine, immunisation, cervical screening, colposcopy, loop excision

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62 **Tweetable Abstract:** Colposcopy referral criteria and service planning need attention following HPV

63 immunisation programme

64

65 **Introduction**

66 Immunisation against the two human papillomavirus (HPV) genotypes, 16 and 18 promises a substantial
67 reduction in high grade cervical intra-epithelial neoplasia (CIN) by 67% and cervical cancers by 70%¹. These
68 predictions assume high vaccine uptake and maintenance of existing cervical screening. Data from Australia²
69 indicated a significant decrease in high grade cervical cytology in women vaccinated before the age of 18
70 years. The realisation of such benefits implies reduced demand for related clinical services.

71

72 In the UK, routine HPV vaccination of girls aged 12-13 in school started in 2008, together with a 3 year 'catch-
73 up' programme for girls up to 18 years designed to expand the immunised cohort and reduce the lag time to
74 benefit from vaccination³. Uptake rates for 3 doses in Scotland are almost 90% of girls routinely immunised in
75 the school and 65.5% in catch-up⁴ with equitable uptake by deprivation score⁵.

76

77 At the time of this study, women became eligible for cervical screening in Scotland at age 20. Women offered
78 immunisation in the catch up programme therefore became eligible for screening in 2010.. Scottish data from
79 the catch-up cohort shows reduced prevalence of HPV16/18 in women aged 20 (29.8% to 13.6%)⁷ and also of
80 high risk HPV types, 31, 33 and 45, suggesting cross protection⁷. A significant reduction in CIN 1 (RR 0.71), CIN
81 2 (RR 0.5) and CIN 3 (RR 0.45) was observed in fully vaccinated women compared with unvaccinated women⁸.
82 Furthermore, there is a reduction of HPV16/18 in unvaccinated 20 year olds whose peers were vaccinated.⁷

83 While this is encouraging, reduced HPV and CIN prevalence has implications for screening. We demonstrated
84 that the predictive values of abnormal cytology for CIN have reduced in immunised women, with a
85 concomitant significant increase in the referral value (the number of women referred to colposcopy on the
86 basis of abnormal cytology to detect a case of CIN2+) by 38%⁹.

87

88 To inform colposcopy service provision as part of a national programme, we measured changes in the referral
89 and colposcopy activity patterns at a population level using routinely collected data in a cohort of women
90 offered catch up HPV vaccination. We aimed to monitor the pattern of new referrals to colposcopy; rates of
91 interventions; the positive predictive value (PPV) of colposcopic impression for high grade CIN; the negative

92 biopsy rate and the rate of default , among young women with increasing rates of HPV vaccination over a
93 period of observation.

94

95 **Methods**

96 We conducted an observational study using national data. Up to 6/6/2016, the eligible population for the
97 Scottish Cervical Screening programme was women aged 20-60 years with 3 yearly screening using liquid
98 based cytology. Referral to colposcopy is based on a single high grade result or repeated low grade or
99 borderline nuclear abnormalities. HPV testing is not used for screening or triage of low grade disease.
100 Colposcopy data are collected routinely for all women referred to colposcopy in NHS Scotland via the National
101 Colposcopy Clinical Information and Audit System (NCCIAS), This is a web-based system which includes
102 women referred to colposcopy with either abnormal cytology from the screening programme or on clinical
103 grounds (with no cytology or normal cytology). Information is episode based and includes patient
104 demographics, appointment details (including attendance/default), clinical data including indication for
105 referral (e.g. abnormal cytology, clinical signs and symptoms), colposcopy assessment and findings, biopsy
106 results, cytology results, treatment methods and the follow-up management plan. Data entry and quality
107 checks are conducted locally and the data are routinely used to produce clinic correspondence to referring
108 practitioners and to women, to monitor colposcopy performance for British Society for Colposcopy and
109 Cervical Pathology (BSCCP) accreditation¹⁰ and to bench mark key performance indicators as part of quality
110 assurance of Scottish colposcopy services.

111

112 We obtained a NCCIAS data extract from NHS Scotland Information and Statistics Division (ISD), which
113 contained the records for all women whose date of birth was on or after 1 January 1985 and who were
114 referred to colposcopy in Scotland 2008-2014 inclusive. Data was anonymised by ISD. The analysis was
115 restricted to those referred for colposcopy at age 20 or 21 to increase the likelihood of women being seen at
116 colposcopy following their initial cervical screen. The performance of colposcopy was assessed by calculating
117 the sensitivity, specificity, PPV and negative predictive value (NPV) with the definitive histology result. Women
118 with normal colposcopy were assumed to have no disease at the time of examination. Performance was
119 calculated at two different cut-offs of disease outcome: for CIN2+ and for any grade of CIN. Evidence of a

120 linear change in performance indicators and proportions over all time points was assessed by logistic
121 regression. As a number of models were run, an adjustment for multiple testing, using the Benjamini-Hochberg
122 false discovery rate procedure was applied, separately to each table, to the traditionally used significance cut-
123 off point of $\alpha=0.05$. This leads to stricter criteria for declaring statistically significant results and the clinical
124 significance of all results was also considered. All statistical analysis was conducted in R (R Core Team (2015)),
125 version 3.1.

126

127 **Results**

128 ***Pattern of referrals***

129 During 2008-2014, there were a total of 31,634 new episodes recorded for women referred to colposcopy with
130 7372 unique women referred for colposcopy at age 20 or 21 (age 20: 3337, age 21: 4035). The number of
131 referrals decreased over the period of observation (See Table 1). There was a non-significant downward trend
132 in the proportion referred with an abnormal screening smear (2008/9; 1294 (91.0%), 2013/14; 758 (90.3%);
133 linear trend p value = 0.03). Whilst the absolute numbers declined, the proportion with borderline nuclear
134 abnormalities (BNA) and low grade dyskaryosis increased with a corresponding reduction in the proportion of
135 women referred with high-grade dyskaryosis and any grade of dyskaryosis (2008/9; 41.2%, 2013/14; 30.7%;
136 linear trend p value =0.01). The number of women with high grade dyskaryosis had more than halved from
137 533 in 2008/9 to 233 in 2013/14, though the 2008/09 figure is potentially an outlier. Women are also referred
138 to colposcopy out with the screening programme for clinical reasons. For these women, there was an increase
139 in the proportion referred to colposcopy with a clinically suspicious cervix (2008/9; 1.6%, 2013/14; 3.1%, linear
140 trend (p = 0.02) but there was no change in the presence of any specific gynaecological symptom (e.g.
141 intermenstrual bleeding (IMB) or post-coital bleeding (PCB) (See Table 1).

142

143 ***Rates of diagnostic and therapeutic interventions***

144 Table 2 shows data from 7013 individual women aged 20-21 who had a colposcopy examination during 2008-
145 2014. The full data set is available in Table S1. Women with a colposcopically normal cervix, assessed by the
146 absence of abnormal colposcopic features (no acetowhite; no capillary vessel patterns (mosaic and/or
147 punctation) or no abnormal vessels), increased (2008/9: 138 (10.3%), 2013/14; 112 (14.0%); linear trend p

148 value =0.002) while the proportion with a colposcopic impression of high-grade CIN decreased (2008/9; 458
149 (34.1%), 2013/14; 217 (27.0%); linear trend p value =0.004). We note that the major change takes place in
150 2012/13. Over the period of observation, the proportion of women having no clinical interventions (biopsy or
151 treatment) increased (2008/9; 19.5%, 2013/14; 26.9%, linear trend p value <0.0001). The proportion having
152 diagnostic punch biopsy/biopsies or treatment (most commonly loop excision or cold coagulation (also known
153 as thermocoagulation)) decreased with the number of therapeutic procedures falling from 318 in 2008/9 to 62
154 in 2013/14. However, we observed an unexpected increase in the proportion of women having a cytology test
155 performed at colposcopy (2008/9; 4.2%, 2013/14; 5.6%, linear trend p value = 0.02).

156

157 ***Performance of colposcopy: PPV, sensitivity and specificity for high grade CIN on histology***

158 The number and proportion of women with high grade disease (CIN2+) confirmed on histology decreased
159 significantly (2008/9; 527 (39.2%), 2013/14; 207 (25.8%), linear trend p value <0.0001). Table 3 shows the
160 performance of colposcopy to predict or exclude CIN. The PPV of colposcopy for CIN2 or worse (CIN2+) on
161 biopsy decreased significantly from 79% in 2008/9 to 67% in 2013/14 (linear trend p value =0.0002), though
162 with the main change associated with 2013/14. The PPV of colposcopy for any grade of CIN or more (CIN+) on
163 biopsy was relatively unchanged, 84% in 2008/9 and 80% in 2013/14 (linear trend p value = 0.32). We did not
164 find any significant change in sensitivity and specificity of colposcopy to predict CIN2+ on biopsy over the
165 period assessed.

166

167 ***Negative biopsy rate***

168 During 2008-2014, 5535 women aged 20-21 had a biopsy performed at colposcopy visit. The negative biopsy
169 rate, calculated as the proportion of women who had a biopsy taken but the histology reported as normal or
170 no CIN, showed no significant change over the period of observation (2008/9; 23.8%, 2009/10; 28.0 %,
171 2010/11;25.0%, 2011/12; 25.8 %, 2012/13; 25.2% and 2013/14;27.8% linear trend p value = 0.4).

172

173 ***Default from first attendance at colposcopy rate***

174 The majority of the women (93.9%) attended their first colposcopy appointment within three months from
175 their date of referral (or date screening cytology reported on SCCRS). Table 4 shows the attendance and

176 default rates for colposcopy. The proportion of women who did not attend without prior warning (DNA),
177 calculated as the proportion of all women given an appointment, decreased significantly over time
178 (2008/9:26.0%, 2013/14; 17.6%; linear trend p value <0.0001).

179

180 **Discussion**

181 ***Main findings***

182 The results from this ecological population-based study indicate a reduction in the absolute numbers of young
183 women referred to colposcopy from the catch-up cohort offered HPV immunisation. The timeframe of the
184 data collection and the size of the effect suggests that this is likely to be associated with HPV vaccination.
185 Previous studies have confirmed the reduction in HPV vaccine type genotypes and performance of cytology as
186 a consequence of immunisation⁵⁻⁹ flagging up the need to review the screening pathway. This is the first
187 population-based study to demonstrate reduced colposcopy activity and performance. We have also
188 confirmed the reported changes in colposcopy performance linked to vaccine status¹¹. The majority of HPV
189 vaccine impact studies have focused on the effect on circulating HPV types^{6,7,12,13} and screening cytology^{2,}
190^{8,9,12}. The sentinel surveillance system in the United States reported a 26% reduction in HPV16/18 associated
191 CIN2+ following HPV vaccination¹⁴ but did not discuss the impact on service provision..

192

193 Clearly, in countries with both vaccination and cervical screening, the screening programme criteria for referral
194 to colposcopy must be reviewed to ensure effective delivery of colposcopy services and to minimise the
195 disbenefits of over-diagnosis in low risk women. Employing such a risk-stratified approach may further reduce
196 the colposcopy work load with implications for service delivery including recruitment and retention of staff,
197 maintaining quality and performance, and ensuring equitable access for women.

198

199 Although the numbers are small, the proportion of women referred to colposcopy with gynaecological signs,
200 has increased. . Gynaecology services allocate patients with 'red flag' symptoms of cervical cancer to different
201 services which may include colposcopy, general gynaecology, gynaecology/oncology or sexual health. The
202 increase in symptomatic women may be the result of optimising spare colposcopy clinic capacity by accepting
203 referrals which could otherwise be seen at other clinics, rather than being driven by increased suspicion of

204 cervical cancer in this low risk cohort. This would maintain skills and the use of colposcopy clinic capacity, time
205 and staffing, relieving pressure on other gynaecology services.

206

207 The increase in cytology sampling at colposcopy could have two explanations: either a relative increase in the
208 number of women with symptoms who are due for screening; or colposcopists managing their own clinical
209 uncertainty by repeating cytology. The latter is not evidence-based and should be addressed at clinic and
210 national guideline level to avoid unnecessary procedures which are unlikely to contribute effectively to patient
211 management

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213

214 Importantly, we are reporting on women who meet the criteria for colposcopy referral (which include
215 persistent low grade disease) compared with single abnormalities reported in the screened population⁸.

216 Before vaccination, the risk of associated CIN with persistent low grade changes was sufficient to warrant
217 investigation at colposcopy. In our analysis, we identified an increase in women referred with no identifiable
218 CIN This corroborates our previous observation that the referral value of cytology increased in immunised
219 women⁹ strengthening the need to review referral criteria to reflect the reduced risk of underlying CIN.

220 National direction from the screening programme may be necessary to address the issues of referral criteria,
221 capacity and clinical management highlighted by our results.

222

223 ***Strengths and limitations***

224 Our study uses nationwide colposcopy data on all women referred to colposcopy in NHS Scotland- the
225 organised nature of the screening programme advocates that national guidelines are followed, mitigating to an
226 extent the influence of individualised practice. Lead colposcopists are responsible for data entry and quality
227 management of data within NCCIAS¹⁵.

228

229 This is an ecological study but although there is no linkage from NCCIAS to the national immunisation record,
230 the magnitude of the change in activity at colposcopy, the temporal relationship with implementation of
231 immunisation and the effect reported from screening data in Scotland^{7,8,9} indicates that these effects are

232 attributable to HPV immunisation. Although completion of 3 doses has been reported at over 65% in the
233 catch-up cohort, this was highest in those girls vaccinated in school (80% uptake) and lower (30% uptake) in
234 those who had left school⁵. Our data comes from the catch-up programme and the maximum effect, when
235 women vaccinated in the school programme attend screening, is yet to be seen.

236

237 Our results could be affected by a number of possible biases. Following the death of a media celebrity in the
238 UK in 2009, there was an increase in the uptake of screening and detection of CIN and cervical cancer
239 particularly in younger women which was not subsequently sustained¹⁷. This would account for the number
240 of abnormalities detected in 2009 compared with previous or subsequent years. There was national
241 standardisation of referral criteria for low grade dyskaryosis from a single to two consecutive low-grade
242 cytology tests in 2012, bringing two of the larger health boards into alignment with the practice of the
243 remaining 12 Scottish boards. In 2013, cytology terminology changed so 'BNA with koilocytes' were classified
244 as low grade dyskaryosis. This will have altered the reporting profile but would not explain the increase in BNA
245 reports. We have previously reported that the number of young women participating in screening has not
246 decreased in recent years so fewer cases does not reflect lower attendance⁹. The HPV vaccination campaign
247 prompted dissemination of information on HPV and immunisation for girls and parents including in the
248 national media. The effect of these factors cannot be measured in this study.

249

250 ***Interpretation***

251

252 The demand for colposcopy services is influenced by a number of factors including the target screening
253 population, the screening test used, and the referral criteria. Other influences include vaccine uptake rates,
254 the type of vaccine and the dosing schedule as well the health-seeking behaviours of the population.

255 Colposcopy requirements of the screening programme will fall and spare capacity at colposcopy carries a cost
256 to the health service. Using colposcopy services to manage gynaecological conditions may not be the most
257 efficient use of a specialist resource but may allow colposcopists to see sufficient numbers of women to
258 maintain their pattern recognition and operative skills, and assure quality of the service¹⁰. In the UK, the key
259 performance indicator is the positive predictive value (PPV) of colposcopy with the lowest acceptable PPV of

260 colposcopy for high grade CIN set at 65%¹⁸. Our data indicates that the PPV of colposcopy in women aged 20-
261 21 years is now just above this bench mark indicating that the cut-off for referral to colposcopy needs review.
262 Furthermore, this threshold may well be breached with an increasingly vaccinated population. We do not yet
263 have data to support alternative strategies based on vaccination status. This would require robust linked data
264 on vaccination status to implement safely

265

266 In Scotland, the peak prevalence of CIN3 is found in 25-29 year old age band¹⁹ which accounts for almost a
267 third of all cases per annum. The proportion of cases of CIN3 diagnosed in 20-24 year age band represents the
268 2nd highest proportion at 21-24%. As the prevalence of CIN3 continues to fall over the next 5 years in both age
269 groups, we need to ensure that any rationalisation of colposcopy services considers the need to maintain the
270 necessary expertise to diagnose and treat women as part of cervical cancer prevention. Whilst there are a
271 number of new technologies which aim to be an adjuvant to traditional colposcopy^{20,21}, their performance also
272 relies on the prevalence of CIN in the referral population.

273

274 It is inevitable that the anticipated potential of vaccination to reduce cervical cancer in the future will reduce
275 secondary prevention activity; service planning needs to address this foreseeable change. Should colposcopy
276 training and staffing be allowed to undergo attrition, or should the existing clinical capacity be used for other
277 patient groups who would benefit from the same clinical expertise? Whilst colposcopy skills are transferrable
278 to other lower genital tract sites, this will require upskilling for staff who currently only deal with cervical
279 disease.

280

281 **Conclusion**

282 A reduction in colposcopy workload is likely to be related to the HPV immunisation. Review of service
283 provision (including referral criteria) which takes into account the increasing number of vaccinated women who
284 will enter screening is required to ensure the continued delivery of an effective colposcopy service.

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286 Discussion Word count 1338

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290 **Disclosures of interests**

291 The authors declare that they have no conflict of interest.

292

293 **Contribution to authorship**

294 MEC conceived the study, supervised the analysis and prepared the manuscript.

295 JP performed the statistical analysis, contributed to the writing of the methods and results section.

296 KK supervised the statistical analysis and contributed to all drafts of the manuscript

297 CR contributed to the design of the study, supervised the statistical analysis and contributed to all drafts of the

298 manuscript

299 KC contributed to the design of the study, drafts and revisions of the manuscript

300 HC contributed to the design of the study, drafts and revisions of the manuscript

301 SCC had oversight of study conduct and statistical analysis, interpretation of results and critical revision of the

302 manuscript.

303 TP contributed to the interpretation of results and the discussion

304 KP contributed to the interpretation of results and the discussion

305 All authors read and approved the final manuscript.

306

307 **Ethics approval**

308 This study was sponsored by the University of Aberdeen. It received REC approval from North of Scotland REC

309 (11/NS/0022) on 9th September 2011. Approvals were also obtained from the Scottish Colposcopy QA Group

310 and the Caldicott guardians in each Scottish NHS Health Board.

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313

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- 363

	Group 1 N (column %) N=198*	Group 2 N (column %) N=163		Overall N=361
		Vaccinated 67 (41.1)	Unvaccinated 96 (58.9)	
Site				
Site 1	95 (48.0)	53 (79.1)	93 (96.9)	241 (66.8)
Site 2	103 (52.0)	14 (20.9)	3 (3.1)	120 (33.2)
Age at colposcopy				
20 years	42 (21.2)	17 (25.4)	5 (5.2)	64 (17.7)
21 years	33 (16.7)	31 (46.3)	5 (5.2)	69 (19.1)
22 years	29 (14.6)	14 (20.9)	18 (18.8)	61 (16.9)
23 years	39 (19.7)	3 (4.5)	31 (32.3)	73 (20.2)
24 years	40 (20.2)	1 (1.5)	17 (17.7)	58 (16.1)
25 years	15 (7.6)	1 (1.5)	20 (20.8)	36 (10.0)
Mean Age (years)	22.2 (SD 1.6)	21.2(SD 1.0)	23.2 (SD 1.4)	22.3 (SD 1.6)
Referral Cytology				
Borderline	46 (23.2)	19 (28.4)	27 (28.1)	92 (25.5)
Mild dyskaryosis	86 (43.4)	34 (50.7)	28 (29.2)	148 (41.0)
Moderate dyskaryosis	36 (18.2)	12 (17.9)	28 (29.2)	76 (21.1)
Severe dyskaryosis	24 (12.1)	2 (3.0)	11 (11.5)	37 (10.2)
Glandular neoplasia	1 (0.5)	-	2 (2.1)	3 (0.8)
Invasive cancer	1 (0.5)	-	-	1 (0.3)
Missing	4 (2)	-	-	4 (1.1)
Histology				
Biopsy not taken [‡]	61 (30.8)	27 (40.3)	20 (20.8)	108 (29.9)
Normal (No CIN)	19 (9.6)	9 (13.4)	10 (10.4)	38 (10.5)
CIN1	53 (26.8)	18 (26.9)	24 (25.0)	95 (26.3)
CIN2	35 (17.7)	9 (13.4)	23 (24.0)	67 (18.6)
CIN3	24 (12.1)	3 (4.5)	14 (14.6)	41 (11.4)
Invasive squamous 1a1	1 (0.5)	-	1 (1.0)	2 (0.6)
CGIN	2 (1.0)	-	4 (4.2)	6 (1.7)
Unsatisfactory	3 (1.5)	1 (1.5)	-	4 (1.1)

Table 1: Comparison of participant demographics between groups. "Vaccinated" women refer to women who had received 2 or more doses of the HPV vaccination. *Group 1 includes 3 women who reported they had received the HPV vaccine. [‡]All cases where biopsy was not taken were because colposcopic appearances were normal.

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	Unvaccinated n/N (%)	Vaccinated n/N (%)	chi squared p- value* (Pearson unless indicated)
Colposcopic Features			
Acetowhite	231/291 (79.4)	54/70 (77.1)	0.623
Mosaic	129/291 (44.3)	30/70 (42.9)	0.791
Punctation	111/291 (38.1)	27/70 (38.6)	1.00
Atypical Vessels	3/291 (1.0)	1/70 (1.4)	0.589 [†]
Iodine Negative**	101/202 (50.0)	33/59 (55.9)	0.442
Colposcopic Opinion			
High Grade***	99/290 (34.1)	13/66 (19.7)	0.027
Histology****			
CIN2+	103/286 (36.0)	13/69 (18.8)	0.006
CIN1+	179/286 (62.6)	32/69 (46.3)	0.044 [†]

371 Table 2 compares the features seen at colposcopy between all participants regardless of disease status who were
372 vaccinated against HPV 16 and 18, and women who were not. It also compares the colposcopic opinion and histology
373 results between these groups. In patients where biopsies were not taken, they were considered to have no
374 disease.*Pearson's test used unless otherwise indicated. [†]Fisher's exact test used. **in 100 cases, iodine was not used.
375 This was for a variety of reasons including patient allergy or colposcopist preference. ***High grade colposcopic opinion
376 was appearance suggestive of CIN2+. ****Histology results were "unsatisfactory" for 5 unvaccinated and 1 vaccinated
377 therefore were excluded from histology analysis.

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	Unvaccinated (95% CI) N=294	Vaccinated (95% CI) N=67	z-test for difference	HPV 16+ (95% CI) N=142	HPV 16 - (95% CI) N=219	z-test for difference
Sensitivity	69.6 (59.6-78.1)	66.7 (35.4-88.7)	p=0.835	65.8 (53.9-76.0)	76.3 (59.4-88.0)	p=0.251
Specificity	86.3 (80.2-90.7)	92.5 (80.9-97.6)	p=0.228	75.0 (62.3-84.6)	92.4 (87.1-95.7)	p<0.001
PPV	74.0 (63.8-82.1)	66.7 (35.4-88.7)	p=0.591	75.8 (63.4-85.1)	69.0 (52.8-81.9)	p=0.443
NPV	83.5 (77.3-88.4)	92.5 (80.9-97.6)	p=0.103	64.9 (52.8-75.4)	94.6 (89.7-97.3)	p<0.001

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Table 3: Predictive values of colposcopy for detecting high grade disease where histology results were considered "gold standard" and the test was colposcopic opinion. This has been done to compare predictive values between vaccinated and unvaccinated participants and between participants who are HPV 16 positive and negative.