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

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Running title
Reduced Scottish colposcopy activity after HPV vaccination
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
to be planned carefully taking account of the increasing number of HPV-immunised women that will be entering cervical screening programmes worldwide.

Word count 249

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

**Tweetable Abstract:** Colposcopy referral criteria and service planning need attention following HPV immunisation programme
Introduction

Immunisation against the two human papillomavirus (HPV) genotypes, 16 and 18 promises a substantial reduction in high grade cervical intra-epithelial neoplasia (CIN) by 67% and cervical cancers by 70%\(^1\). These predictions assume high vaccine uptake and maintenance of existing cervical screening. Data from Australia\(^2\) indicated a significant decrease in high grade cervical cytology in women vaccinated before the age of 18 years. The realisation of such benefits implies reduced demand for related clinical services.

In the UK, routine HPV vaccination of girls aged 12-13 in school started in 2008, together with a 3 year ‘catch-up’ programme for girls up to 18 years designed to expand the immunised cohort and reduce the lag time to benefit from vaccination\(^3\). Uptake rates for 3 doses in Scotland are almost 90% of girls routinely immunised in the school and 65.5% in catch-up\(^4\) with equitable uptake by deprivation score\(^5\).

At the time of this study, women became eligible for cervical screening in Scotland at age 20. Women offered immunisation in the catch up programme therefore became eligible for screening in 2010. Scottish data from the catch-up cohort shows reduced prevalence of HPV16/18 in women aged 20 (29.8% to 13.6%)\(^7\) and also of high risk HPV types, 31, 33 and 45, suggesting cross protection\(^7\). A significant reduction in CIN 1 (RR 0.71), CIN 2 (RR 0.5) and CIN 3 (RR 0.45) was observed in fully vaccinated women compared with unvaccinated women\(^8\). Furthermore, there is a reduction of HPV16/18 in unvaccinated 20 year olds whose peers were vaccinated\(^7\).

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

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

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

We obtained a NCCIAS data extract from NHS Scotland Information and Statistics Division (ISD), which
contained the records for all women whose date of birth was on or after 1 January 1985 and who were
referred to colposcopy in Scotland 2008-2014 inclusive. Data was anonymised by ISD. The analysis was
restricted to those referred for colposcopy at age 20 or 21 to increase the likelihood of women being seen at
colposcopy following their initial cervical screen. The performance of colposcopy was assessed by calculating
the sensitivity, specificity, PPV and negative predictive value (NPV) with the definitive histology result. Women
with normal colposcopy were assumed to have no disease at the time of examination. Performance was
 calculated at two different cut-offs of disease outcome: for CIN2+ and for any grade of CIN. Evidence of a
linear change in performance indicators and proportions over all time points was assessed by logistic
regression. As a number of models were run, an adjustment for multiple testing, using the Benjamini-Hochberg
false discovery rate procedure was applied, separately to each table, to the traditionally used significance cut-
off point of alpha=0.05. This leads to stricter criteria for declaring statistically significant results and the clinical
significance of all results was also considered. All statistical analysis was conducted in R (R Core Team (2015)),
version 3.1.

Results

Pattern of referrals

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

Rates of diagnostic and therapeutic interventions

Table 2 shows data from 7013 individual women aged 20-21 who had a colposcopy examination during 2008-
2014. The full data set is available in Table S1. Women with a colposcopically normal cervix, assessed by the
absence of abnormal colposcopic features (no acetowhite; no capillary vessel patterns (mosaic and/or
punctuation) or no abnormal vessels), increased (2008/9: 138 (10.3%), 2013/14; 112 (14.0%); linear trend p
value =0.002) while the proportion with a colposcopic impression of high-grade CIN decreased (2008/9; 458 (34.1%), 2013/14; 217 (27.0%); linear trend p value =0.004). We note that the major change takes place in 2012/13. Over the period of observation, the proportion of women having no clinical interventions (biopsy or treatment) increased (2008/9; 19.5%, 2013/14; 26.9%, linear trend p value <0.0001). The proportion having diagnostic punch biopsy/biopsies or treatment (most commonly loop excision or cold coagulation (also known as thermocoagulation)) decreased with the number of therapeutic procedures falling from 318 in 2008/9 to 62 in 2013/14. However, we observed an unexpected increase in the proportion of women having a cytology test performed at colposcopy (2008/9; 4.2%, 2013/14; 5.6%, linear trend p value = 0.02).

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

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

Negative biopsy rate

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

Default from first attendance at colposcopy rate

The majority of the women (93.9%) attended their first colposcopy appointment within three months from their date of referral (or date screening cytology reported on SCCRS). Table 4 shows the attendance and
default rates for colposcopy. The proportion of women who did not attend without prior warning (DNA),
calculated as the proportion of all women given an appointment, decreased significantly over time
(2008/9: 26.0%, 2013/14: 17.6%; linear trend p value <0.0001).

Discussion

Main findings

The results from this ecological population-based study indicate a reduction in the absolute numbers of young
women referred to colposcopy from the catch-up cohort offered HPV immunisation. The timeframe of the
data collection and the size of the effect suggests that this is likely to be associated with HPV vaccination.
Previous studies have confirmed the reduction in HPV vaccine type genotypes and performance of cytology as
a consequence of immunisation 5-9 flagging up the need to review the screening pathway. This is the first
population-based study to demonstrate reduced colposcopy activity and performance. We have also
confirmed the reported changes in colposcopy performance linked to vaccine status11. The majority of HPV
vaccine impact studies have focused on the effect on circulating HPV types 6,7, 12, 13 and screening cytology 2.
8,9,12. The sentinel surveillance system in the United States reported a 26% reduction in HPV16/18 associated
CIN2+ following HPV vaccination14 but did not discuss the impact on service provision..

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

Although the numbers are small, the proportion of women referred to colposcopy with gynaecological signs,
has increased. Gynaecology services allocate patients with ‘red flag’ symptoms of cervical cancer to different
services which may include colposcopy, general gynaecology, gynaecology/oncology or sexual health. The
increase in symptomatic women may be the result of optimising spare colposcopy clinic capacity by accepting
referrals which could otherwise be seen at other clinics, rather than being driven by increased suspicion of
cervical cancer in this low risk cohort. This would maintain skills and the use of colposcopy clinic capacity, time and staffing, relieving pressure on other gynaecology services.

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

Importantly, we are reporting on women who meet the criteria for colposcopy referral (which include persistent low grade disease) compared with single abnormalities reported in the screened population. Before vaccination, the risk of associated CIN with persistent low grade changes was sufficient to warrant investigation at colposcopy. In our analysis, we identified an increase in women referred with no identifiable CIN. This corroborates our previous observation that the referral value of cytology increased in immunised women strengthening the need to review referral criteria to reflect the reduced risk of underlying CIN. National direction from the screening programme may be necessary to address the issues of referral criteria, capacity and clinical management highlighted by our results.

**Strengths and limitations**

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

This is an ecological study but although there is no linkage from NCCIAS to the national immunisation record, the magnitude of the change in activity at colposcopy, the temporal relationship with implementation of immunisation and the effect reported from screening data in Scotland indicates that these effects are
attributable to HPV immunisation. Although completion of 3 doses has been reported at over 65% in the
catch-up cohort, this was highest in those girls vaccinated in school (80% uptake) and lower (30% uptake) in
those who had left school\(^5\). Our data comes from the catch-up programme and the maximum effect, when
women vaccinated in the school programme attend screening, is yet to be seen.

Our results could be affected by a number of possible biases. Following the death of a media celebrity in the
UK in 2009, there was an increase in the uptake of screening and detection of CIN and cervical cancer
particularly in younger women which was not subsequently sustained \(^7\). This would account for the number
of abnormalities detected in 2009 compared with previous or subsequent years. There was national
standardisation of referral criteria for low grade dyskaryosis from a single to two consecutive low-grade
cytology tests in 2012, bringing two of the larger health boards into alignment with the practice of the
remaining 12 Scottish boards. In 2013, cytology terminology changed so ‘BNA with koilocytes’ were classified
as low grade dyskaryosis. This will have altered the reporting profile but would not explain the increase in BNA
reports. We have previously reported that the number of young women participating in screening has not
decreased in recent years so fewer cases does not reflect lower attendance \(^9\). The HPV vaccination campaign
prompted dissemination of information on HPV and immunisation for girls and parents including in the
national media. The effect of these factors cannot be measured in this study.

**Interpretation**

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

Colposcopy requirements of the screening programme will fall and spare capacity at colposcopy carries a cost
to the health service. Using colposcopy services to manage gynaecological conditions may not be the most
efficient use of a specialist resource but may allow colposcopists to see sufficient numbers of women to
maintain their pattern recognition and operative skills, and assure quality of the service \(^10\). In the UK, the key
performance indicator is the positive predictive value (PPV) of colposcopy with the lowest acceptable PPV of
colposcopy for high grade CIN set at 65% \(^18\). Our data indicates that the PPV of colposcopy in women aged 20-21 years is now just above this benchmark indicating that the cut-off for referral to colposcopy needs review. Furthermore, this threshold may well be breached with an increasingly vaccinated population. We do not yet have data to support alternative strategies based on vaccination status. This would require robust linked data on vaccination status to implement safely.

In Scotland, the peak prevalence of CIN3 is found in 25-29 year old age band\(^19\) which accounts for almost a third of all cases per annum. The proportion of cases of CIN3 diagnosed in 20-24 year age band represents the 2\(^{nd}\) highest proportion at 21-24%. As the prevalence of CIN3 continues to fall over the next 5 years in both age groups, we need to ensure that any rationalisation of colposcopy services considers the need to maintain the necessary expertise to diagnose and treat women as part of cervical cancer prevention. Whilst there are a number of new technologies which aim to be an adjuvant to traditional colposcopy\(^20,21\), their performance also relies on the prevalence of CIN in the referral population.

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

**Conclusion**

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

The authors declare that they have no conflict of interest.

Contribution to authorship

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

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

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

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

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

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

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

TP contributed to the interpretation of results and the discussion.

KP contributed to the interpretation of results and the discussion.

All authors read and approved the final manuscript.

Ethics approval

This study was sponsored by the University of Aberdeen. It received REC approval from North of Scotland REC (11/NS/0022) on 9th September 2011. Approvals were also obtained from the Scottish Colposcopy QA Group and the Caldicott guardians in each Scottish NHS Health Board.

Funding

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References:

1. Smith JS; Lindsay L; Hoots B; Keys J; Franceschi S; Winer R et al. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis.


<table>
<thead>
<tr>
<th></th>
<th>Group 1 N (column %)</th>
<th>Group 2 N (column %)</th>
<th>Overall N=361</th>
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<td>N=163</td>
<td></td>
</tr>
<tr>
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<td>53 (79.1)</td>
<td>93 (96.9)</td>
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<tr>
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<td>103 (52.0)</td>
<td>14 (20.9)</td>
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<td>20 years</td>
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<td>23.2 (SD 1.4)</td>
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<td>-</td>
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<td>-</td>
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<td>Histology</td>
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<td>27 (40.3)</td>
<td>20 (20.8)</td>
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<td>19 (9.6)</td>
<td>9 (13.4)</td>
<td>10 (10.4)</td>
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<td>CIN1</td>
<td>53 (26.8)</td>
<td>18 (26.9)</td>
<td>24 (25.0)</td>
</tr>
<tr>
<td>CIN2</td>
<td>35 (17.7)</td>
<td>9 (13.4)</td>
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<td>CIN3</td>
<td>24 (12.1)</td>
<td>3 (4.5)</td>
<td>14 (14.6)</td>
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<tr>
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<tr>
<td>CGIN</td>
<td>2 (1.0)</td>
<td>-</td>
<td>4 (4.2)</td>
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<tr>
<td>Unsatisfactory</td>
<td>3 (1.5)</td>
<td>1 (1.5)</td>
<td>-</td>
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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.
<table>
<thead>
<tr>
<th>Colposcopic Features</th>
<th>Unvaccinated n/N (%)</th>
<th>Vaccinated n/N (%)</th>
<th>chi squared p-value* (Pearson unless indicated)</th>
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<tr>
<td>Acetowhite</td>
<td>231/291 (79.4)</td>
<td>54/70 (77.1)</td>
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<td>Mosaic</td>
<td>129/291 (44.3)</td>
<td>30/70 (42.9)</td>
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<td>Punctation</td>
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<td>27/70 (38.6)</td>
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<td>Atypical Vessels</td>
<td>3/291 (1.0)</td>
<td>1/70 (1.4)</td>
<td>0.589*</td>
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<td>Iodine Negative**</td>
<td>101/202 (50.0)</td>
<td>33/59 (55.9)</td>
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<td>Colposcopic Opinion</td>
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<tr>
<td>High Grade***</td>
<td>99/290 (34.1)</td>
<td>13/66 (19.7)</td>
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<td>Histology****</td>
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<tr>
<td>CIN2+</td>
<td>103/286 (36.0)</td>
<td>13/69 (18.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>CIN1+</td>
<td>179/286 (62.6)</td>
<td>32/69 (46.3)</td>
<td>0.044*</td>
</tr>
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</table>

Table 2 compares the features seen at colposcopy between all participants regardless of disease status who were vaccinated against HPV 16 and 18, and women who were not. It also compares the colposcopic opinion and histology results between these groups. In patients where biopsies were not taken, they were considered to have no disease. *Pearson’s test used unless otherwise indicated. *Fisher’s exact test used. **In 100 cases, iodine was not used. ***High grade colposcopic opinion was appearance suggestive of CIN2+. ****Histology results were “unsatisfactory” for 5 unvaccinated and 1 vaccinated therefore were excluded from histology analysis.
<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated (95% CI)</th>
<th>Vaccinated (95% CI)</th>
<th>z-test for difference</th>
<th>HPV 16+ (95% CI)</th>
<th>HPV 16 - (95% CI)</th>
<th>z-test for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=294</td>
<td>N=67</td>
<td></td>
<td>N=142</td>
<td>N=219</td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>69.6 (59.6-78.1)</td>
<td>66.7 (35.4-88.7)</td>
<td>p=0.835</td>
<td>65.8 (53.9-76.0)</td>
<td>76.3 (59.4-88.0)</td>
<td>p=0.251</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>86.3 (80.2-90.7)</td>
<td>92.5 (80.9-97.6)</td>
<td>p=0.228</td>
<td>75.0 (62.3-84.6)</td>
<td>92.4 (87.1-95.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>74.0 (63.8-82.1)</td>
<td>66.7 (35.4-88.7)</td>
<td>p=0.591</td>
<td>75.8 (63.4-85.1)</td>
<td>69.0 (52.8-81.9)</td>
<td>p=0.443</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>83.5 (77.3-88.4)</td>
<td>92.5 (80.9-97.6)</td>
<td>p=0.103</td>
<td>64.9 (52.8-75.4)</td>
<td>94.6 (89.7-97.3)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

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.