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RESEARCH ARTICLE

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Clinical performance of primary HPV screening cut-off for colposcopy referrals in HPV-vaccinated cohort: Observational study

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Abstract

Objective: To understand the effect of changing from cytology-based to primary HPV screening on the positive predictive value (PPV) of colposcopy referrals for cervical intraepithelial neoplasia (CIN) in a cohort offered HPV vaccination.

Design: Retrospective pre/post observational cohort study.

Setting: Scotland.

Population or sample: 2193 women referred to colposcopy between September 2019 and February 2020 from cytology-based screening and between September 2020 and February 2021 from primary high-risk HPV (hrHPV) screening.

Methods: Calculating positive predictive values (PPVs) for two cohorts of women; one having liquid-based cytology screening and the other, the subsequent hrHPV cervical screening as a pre/post observational study.

Main outcome measures: Positive predictive values of LBC and hrHPV cut-offs for colposcopy referral for CIN at colposcopy.

Results: Three papers fitted our criteria; these reported results only for cytology-based screening. The PPV was lower for women in HPV-vaccinated cohorts indicating a lower prevalence of disease. Vaccination under the age of 17 had the lowest PPV reported. Scottish colposcopy data concerning hrHPV and cytology showed a non-significant difference between PPV (17.5%, 95% CI 14.3–20.7, and 20.6, 95% CI 16.7–24.5, respectively) for referrals with a cut-off of low grade dyskaryosis (LGD); both met the standard set of 8–25%. The hrHPV PPV (66.7, 95% CI 56.8–76.6) was comparable to cytology (64.1, 95% CI 55.8–72.4) for referrals with a cut-off of high grade dyskaryosis (HGD) but neither met the standard set of 77–92%.

Conclusions: Current literature only provides PPVs for LBC and, overall, the vaccinated cohort had lower PPVs. Only LG dyskaryosis met PHE criteria. The PPV for HPV-vaccinated women undergoing either LBC or HR-HPV screening were not statistically different. However, similar to papers in the current literature, HG dyskaryosis (HGD) PPVs of both techniques did not meet the PHE threshold of 76.6–91.6% outlined in the cervical standards data report.

KEYWORDS
cervical screening, colposcopy, HPV, HPV vaccine

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1 | INTRODUCTION

The Scottish Cervical screening programme changed from cervical cytology to high-risk human papillomavirus (hrHPV)-based screening with cytology triage in 2020 following the recommendation of the UK National Screening Committee (UK NSC) based on evidence to reduce the risk of cervical cancer further through increased sensitivity for cervical disease.[1] The screening intervals for testing were extended from 3 to 5 years for women who test hrHPV-negative as a result of the high negative predictive value for high grade cervical intraepithelial neoplasia (CIN).[2] However, this contrasts with a lower PPV, which can lead to higher referral rates to colposcopy, possible over-investigation and even over-treatment of hrHPV-positive women.[3]

The specific definition of PPV in relation to cervical screening is laid out by Public Health England (PHE) as 'The proportion of women referred with high grade abnormalities who have a histological outcome of CIN2, CIN3, adenocarcinoma in situ/CGIN or cervical cancer'.[4] PPV is also directly affected by the prevalence of disease in women who are being screened.[4] PHE outlined that the PPV for screening HGD should range between 76.6% and 91.6%. For low grade dyskaryosis (LGD) this should be between 7.0% and 22.9% (referred to as abnormal predictive value [APV]). PPV is directly affected by the prevalence of disease in women who are being screened and can be impacted by vaccination against HPV.[4]

Since 2008, the UK has offered HPV vaccination to girls from the age of 12 with a catch-up programme in 2008–2010 to vaccinate older girls between 13 and 17 and introducing a gender-neutral programme in 2019. Scotland has maintained a high uptake of the HPV vaccine.[5] The implementation of a nationwide vaccination programme with sustained high uptake has seen a significant statistical and clinical impact; as the cohort offered vaccination reach the age threshold for screening, the rates of colposcopy referrals and incidence of CIN has decreased.[6]

In Scotland the use of HPV primary testing was due to replace liquid-based cytology (LBC) in March 2020.[7] However, due to the Covid-19 pandemic the screening of women was paused, with full recommencement of the programme occurring September 2020.[8] All Scottish colposcopy clinics store clinical data on NCCIAS to allow for retrospective data interpretation for audit and bench marking as well as routine administration.[9] With the increase of HPV-vaccinated women with falling CIN incidence, a preliminary accuracy assessment of the new challenges to colposcopy services is needed for service planning and review of referral criteria to ensure the referral population is appropriate based on risk. We undertook a review on the current literature available on primary HPV screening performance compared with cytology and an observational pre/post study of PPV of referrals to colposcopy before and after the programme in the cohort offered HPV vaccination.

2 | METHODS

A data report of women aged 25–29, screened between 1 September 2019 and 29 February 2020 (Cytology-based programme) and between 1 September 2020 and 28 February 2021 (Primary HPV screening with cytology triage) were extracted from NCCIAS. New outpatient attendances were recorded and referred to colposcopy where referral cytology was LGD or high grade dyskaryosis (HGD). The histological outcome related to these cytology referrals was recorded where available. Referrals with no cytology or negative, unsatisfactory, glandular abnormality or other malignancy cytology referrals were excluded from analysis. Histological outcomes included normal, CIN1, CIN2/CIN3, invasive squamous, CGIN and invasive adenocarcinoma. PPV was calculated according to Palmer et al.[10] Confidence intervals of 95% (95% CI) were determined through statistical analysis following van Zaane et al.[11]

The p-value was obtained for LBC and hrHPV datasets using Two-Factor analysis of variance (ANOVA) without replication, using Microsoft EXCEL, and was performed on the total new out-patient attendances of the referral cytology categories used in the study (borderline change in squamous cells, low grade dyskaryosis, high grade dyskaryosis (moderate), high grade dyskaryosis (severe), high grade dyskaryosis?, invasive and borderline change in endocervical cells).

3 | RESULTS

3.1 | Scottish PPV values—primary HPV screening versus cytology

Between 1 September 2019 and 29 February 2020 a total of 1016 women between 25 and 29 attended colposcopy as new referrals based on their cytology result. During the same amount of time between 2020 and 2021, 1177 new attendees were recorded. Statistical analysis of data showed no significant difference in total new attendance between the groups in distribution and mean LBC and hrHPV groups ($p = 0.34$).

3.2 | PPV of cytology versus HPV primary screening

The PPV calculated shows that in referrals with LGD during a 6-month interval, LBC was higher than hrHPV by 3.1% (see Table 1). However, both were within acceptable PHE limits. In the high-grade cytology for CIN2$^+$, LBC (64.1%) had a lower value than HPV$^+$/HGD dyskaryosis referrals (66.7%) by 2.6%. Both screening tools were below the PHE cut-off guidance of 76.6%. Confidence intervals would suggest this difference is not significant.

4 | DISCUSSION

To date, PPV of referral to colposcopy has not been reported for an HPV-immunised cohort using hrHPV testing. It has been shown that vaccinated women have a lower PPV than unvaccinated women when tested with the LBC technique[10,12,13] in the previous literature. Scottish data obtained from NCCIAS showed that in a largely vaccinated cohort, the PPV between LBC and hrHPV techniques was not significantly different.

Since its introduction in 2008, the Scottish HPV vaccination programme has had a high uptake of around 90%.[14] Previous studies in Scotland have shown a marked decrease of CIN3 or worse (89% decrease), CIN2 or worse (88%) and CIN1 (79%) in vaccinated girls. There is evidence indicting herd immunity in Scotland of unvaccinated women within the same age-group cohort and lower rates of subsequent CIN when the vaccine is given at a younger age.[15] Lei et al. showed a large drop in PPV of 9.6% in women who received the vaccine, which would suggest that in future the vaccination could lower disease prevalence and burden as more young Scottish women are vaccinated and at an earlier age.

This is corroborated by the current evidence showing that the PPV of screening results for CIN is lower in women who have been vaccinated. This is likely to result from the lower prevalence of CIN in the screened population.[16] In the current literature, reported PPV for HGD in the reviewed literature with LBC screening did not achieve the PHE guideline threshold for vaccinated cohorts and this was confirmed in our own pre/post observational study of Scottish colposcopy data, which was comparable to the published literature of vaccinated women.

Considering the age group of the cohort analysed, the majority would have been vaccinated up to levels that would induce herd immunity.[10] However, there were differences between the LBC and hrHPV values. With low grade cytology, the CIN2$^+$ PPV for both techniques were similar and met the PHE guidelines. High grade cytology of CIN2$^+$ showed that hrHPV screening had a higher PPV than LBC but the 95% confidence intervals showed that this was not significant. Overall, although there was no indication of lower PPV at low and high grade cytology triage in hrHPV screening compared with LBC, the results are reassuring given that the primary HPV programme was rolled out over a year ago.

TABLE 1 Calculated PPV and 95% CI of NCCIAS data obtained of Scottish women 25–29 years of age, from September 2019 to February 2020 (LBC) and from September 2020 to February 2021 (hrHPV)

	PPV CIN2$^+$	95% CI
Low-grade cytology		
LBC	20.6	16.7–24.5
hrHPV	17.5	13.6–19.7
High-grade cytology		
LBC	64.1	55.8–72.4
hrHPV	66.7	56.8–76.6

However, the levels have not met the PHE standard and suggest that there is an over-referral of women to colposcopy.

The risks of investigation and treatment of healthy individuals through punch biopsy or large loop excision are infection or bleeding, which can cause cervical stenosis and other adverse obstetric outcomes.[17,18] Women undergoing colposcopy can also have adverse psychological outcomes; patients have reported moderate to high anxiety and distress over possible diagnosis, reproductive and sexual implications.[18,19] Another difficulty is in retaining colposcopy skills due to an increase in no-disease samples[3,6] and it has been shown that the decrease in expertise can affect biopsy quality and diagnosis.[20]

However, a recent study by Alfonzo et al.[21] suggests that even with an abnormal smear result and normal colposcopy, there was still a risk of CIN2$^+$ of around 5% and abnormal cytology had a high specificity for CIN2$^+$ when paired with the Swede score scale.

Overall, our analysis suggests we are screening women at too young an age if vaccination is reducing disease burden in young Scottish women and that the risk of doing harm to a patient may outweigh the benefits of the screen itself. Although we can be reassured that the current selection of referral to colposcopy has not deteriorated, the anticipated changes in PPV with a lower prevalence of disease warrants continued review.

5 | CONCLUSION

The PPV for the current colposcopy referral criteria does not meet the standards set in the UK and indicates that these need to be revised in view of primary HPV screening and HPV immunisation.

AUTHOR CONTRIBUTIONS

All three authors contributed to the conception, analysis of data, interpretation of data and revision of the article. MB undertook the literature search and drafted the article. MG reviewed the data search, paper selection and edited the article. MEC proposed the study, reviewed the literature search and edited the article.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

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

ETHICS APPROVAL

As this study analysed routinely collected data as part of a service evaluation, ethical approval was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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