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

Marikka Beecroft[1]

Mahalakshmi Gurumurthy[1]

Margaret E Cruickshank[1]

Aberdeen Centre for Women's Health Research (ACWHR)
University of Aberdeen
ABERDEEN
AB25 2ZD

Shortened running title: PPV of HPV screening cut-off for referral in an HPV vaccinated cohort

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 - February 2020 from ~~from~~ cytology-based screening and September 2020 – February 2021 from primary high-risk HPV (hrHPV) screening.

METHODS: Calculating Positive Predictive Values (PPVs) for 2 cohorts of women; one cytology-based screening and the subsequent hrHPV ~~-~~primary 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: There was no significant difference in the PPV between referral from hrHPV and cytology (17.5%, CI 95%=14.3-20.7; 20.6, CI 95%=16.7-24.5) for referrals with a cut-off of low grade dyskaryosis (LGD); both met the Public Health England (PHE) standard set of 8-25%. hrHPV PPV (66.7, CI 95%=56.8-76.6) was comparable to cytology (64.1, CI 95%=55.8-72.4) for referrals with a cut-off of high grade dyskaryosis (HGD) but neither met the PHE standard set of 77-92%.

CONCLUSIONS:

Our results showed that tThe LGD PPV for HPV vaccinated women undergoing either LBC or HR-HPV screening were not statistically different and met the PHE performance criteria. HG dyskaryosis (HGD) PPVs of both techniques were similar indicating that colposcopy is performing in vaccinated cohort screened by hrHPV testing but neither did not meet the PHE threshold of 76.6-91.6% outlined in the cervical standards data report. Further review of cut-off for selection for investigation at colposcopy is needed to ensure appropriate selection on the basis of risk.

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Tweetable abstract: HPV primary screening in HPV vaccinated cohorts merits review of selection based on risk for colposcopy referral.

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 that it will reduce the risk of cervical cancer further through increased sensitivity for cervical disease[1]. The screening intervals for testing was extended from 3 years to 5 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 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].~~

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Since 2008 the UK has offered HPV vaccination to girls from the age of 12 with a catch-up programme 2008-2010 to vaccinate older girls between 13-17 and the introduction of a gender-neutral programme in 2019. Scotland has maintained a high uptake of the HPV ~~vaccine~~immunisation[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 Covid-19 pandemic the screening of women was paused with the 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]. 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 an observational pre/post study of PPV of referrals to colposcopy before and after the programme in the cohort offered HPV vaccination.

Methods

A data report of women from the ages of 25-29 screened between 1st September 2019 - 29th February 2020 (Cytology based programme) and 1st September 2020 - 28th 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 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 as screening aims to detect squamour abnormalities and due to small numbers in these young cohorts. Histological outcomes included normal, CIN1, CIN2/CIN3, Invasive Squamous, CGIN, and Invasive Adenocarcinoma. PPV was calculated according to the Palmer *et al.* 2016 paper[10]. Confidence Intervals of 95% were determined through statistical analysis using van Zaane *et al.* 2012 paper [12].

P-value was obtained for LBC and hrHPV datasets using Two-Factor 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).

Results

Scottish PPV values primary HPV screening vs. cytology

~~In total~~ Bbetween 1st September 2019 and 29th 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~~September 2020 to February ~~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).

PPV of Cytology Vs. HPV Primary Screening

The PPV calculated shows that in referrals with LGD during a six-month interval, LBC was higher than hrHPV by 3.1% (see Table 14). 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 PHE cut-off guidance of 76.6%. Confidence intervals would suggest this difference is not significant.

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 when tested with LBC technique[10,12,13] in 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 and performing to similar standard.

The Scottish HPV vaccination programme since its introduction in 2008 has had a high uptake of around 90%[154]. 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[165]. Lei *et al.* showed a large drop in PPV of 9.6% in women who received the vaccine; 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.

~~The~~ This is corroborated by the current evidence shows 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]. T~~t~~he reported PPV for of HGD, in the reviewed literature with LBC screening, did not achieve~~d~~ the PHE guideline threshold for vaccinated cohorts and this was confirmed in our own pre/post observational study of Scottish colposcopy data which were comparable to published literature of vaccinated women.

Considering the age group of the cohort analysed, the majority of them would have been vaccinated and to a level~~s~~ that would induce herd-immunity[10]. However, there were differences between the LBC and hrHPV values. In low grade cytology for CIN2+ PPV for both techniques were similar and met the PHE guidelines. High grade cytology of CIN2+ showed hrHPV screening had a higher PPV than LBC but, 95% CI showed this was not significant. Overall, whilst there was no indication of lower PPV at low and high grade cytology triage in hrHPV screening compared with LBC, it is reassuring given that the primary HPV programme has rolled out over a year ago. However, the levels have not met the PHE standard and indicate 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 or ~~which can cause~~ cervical stenosis and other adverse obstetric outcomes[178,198]. 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[1920]. 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[210]. However, a recent study by Alfonzo *et al.* suggests that even with an abnormal smear result and normal colposcopy, there was still a risk of CIN2+ of around 5% and it had a high specificity for CIN2+ when paired with the Swede score scale.

Overall, this suggests we are screening women at too young an age if vaccination is reducing disease burden in young Scottish women and that the risk to do harm to a patient may outweigh the benefits of the screen itself. Whilst we can be reassured that current selection of referral to colposcopy has not deteriorated and colposcopy performance is being sustained, the anticipated changes in PPV with lower prevalence of disease warrants continued review. As more data on performance of HPV screening programmes in vaccinated cohorts accumulates, we need to ensure that we are selecting women at a level of risk of CIN that warrents colposcopy and its associated interventions; this includes age to start screening,

screening intervals and the cut-off criteria on the basis of primary screening and any triage tests.

Conclusion

The PPV for the current colposcopy referral criteria have not fallen in the cohort vaccinated and screened by hrHPV testing. However, this 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.

Disclosure of Interests

The authors have no disclosures of interest to report

Contributions to Authorship

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

Ethics Approval

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

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