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**ABSTRACT**

**Objective:** To assess the effectiveness of an HPV vaccination programme in reducing the risk of cervical abnormalities identified at subsequent screening.

**Design:** Retrospective cohort study using administrative health data.

**Setting:** General population of Ferrara Province, Italy.

**Population:** Female residents born in 1986-1993 and participating in the organized cervical screening programme in 2011-2018, who were eligible for HPV vaccination in catch-up cohorts.

**Methods:** Logistic regression to evaluate the potential association between abnormal cervical cytology and one, two, three or at least one dose of HPV vaccine.

**Main outcome measures:** Cervical abnormalities, as predicted by low-grade or high-grade cytology, by number of vaccine doses, stratified by age.

**Results:** The sample consisted of 7,785 women (mean age 27.5 years, SD 2.3). Overall, 391 (5.0%) were vaccinated with ≥1 dose, and 893 (11.5%) had abnormal cytology. Women receiving at least one vaccine dose were significantly less likely to have an abnormal cytology (adjusted odds ratio 0.52; 95% confidence interval 0.34 to 0.79). Similar results were observed for women receiving a single dose, for both bivalent and quadrivalent vaccines, and applying buffer periods (excluding cytological outcomes within one month, six months, and one year of the first dose).

**Conclusions:** In the context of an organised cervical screening programme in Italy, catch-up HPV vaccination almost halved the risk of cytological abnormalities.

**Funding:** None was received.

**Keywords:** Human papillomavirus; vaccine; cervical screening.

**Tweetable abstract**

Among Ferrara women, vaccination against human papillomavirus halved the risk of screening cervical abnormalities.

**INTRODUCTION**

Cervical cancer, caused by persistent infection with oncogenic human papillomavirus (HPV),[1] is the fourth most frequently diagnosed cancer among women worldwide.[2] Screening programmes have repeatedly shown their effectiveness in reducing the burden of disease,[3] while HPV vaccination programmes are now impacting infection prevalence, colposcopy referral rates and detection of pre-cancerous lesions.[4, 5]

The Italian National Health System has offered cervical screening programmes since 1996,[6] and recommended HPV vaccination to all 12-year old girls since 2007, spurring the gradual introduction of vaccination programmes.[7] However, no study has yet evaluated the effectiveness of vaccination within screening programmes .

The present study aimed to assess the population-based effectiveness of HPV vaccination in reducing the risk of abnormal cytology identified at cervical screening in the Province of Ferrara, Italy.

## METHODS

**Ferrara cervical cancer prevention programmes.** The organised cervical screening programme commenced in 1997, and currently offers liquid based cytology (LBC) testing every three years to women aged 25-29-years old, and HPV DNA testing every five years to women aged 30-64-years.[8] Colposcopy is the second level diagnostic test for women with positive cytology (atypical squamous cells of undetermined significance and worse - ASC-US+), or positive HPV DNA tests with positive reflex LBC.[8] The HPV voluntary vaccination programme started in 2009, offering three doses of either bivalent or quadrivalent vaccines [9, 10] to 12-13-year old females for free, while catch-up vaccination required co-payment for 14-19-year olds, and self-payment for older women.[11] In the province, the overall screening uptake was 66% from 2014 to 2017,[12] and the vaccination uptake was 17.2% for birth cohorts 1990 to 1995.[13]

Both vaccination and screening programmes are managed by the Local Health Agency, which stores comprehensive vaccination and screening data in administrative datasets, with encrypted fiscal code as a unique lifetime identifier. Deterministic linkage of vaccination and screening data was performed using this code, without any direct participation of patients or the public in the study.

**Study cohorts.** We included all the residents of the birth cohorts 1986 to 1993, with at least one satisfactory cytology test (meeting the minimum squamous cellularity requirements, according to the 2001 Bethesda System)[14] performed between January 1st 2011 and December 27th 2018. Non-residents were excluded because information on vaccination status was not available (Figure 1). Figure S1 summarizes eligibility for vaccination and the number of screening rounds provided to the women in the study period. It should be noted that the included women were eligible for catch-up HPV vaccination from the age of 14-years to over 30, and therefore constituted most likely a 'post exposure' group.

The number of female residents (on January 1st 2018) was obtained from the National Institute of Statistics.[15] Vaccination status and dates of each dose, year and country of birth, residential area, and cytology results were obtained from Local Health Agency registries. All cervical cytology samples were analyzed at the Ferrara Hospital Pathology Laboratory (Arcispedale Sant'Anna), and the same

specimen collection technique was used throughout the whole study period. The LBC kit, however, changed from SurePath (BD Diagnostics, Burlington, NC) to ThinPrep (Hologic, Marlborough, MA) in December 2015.

**Outcome and exposure measures.** The main outcome was one LBC with abnormal cytology between January 1st 2011 and December 27th 2018. According to 2001 Bethesda system (Table S1) [8, 14], abnormal cytology included HPV DNA-positive atypical squamous cells of undetermined significance (HPV+ ASC-US), atypical glandular cells (AGC), high-grade atypical squamous cells (ASC-H), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).[14] In the Ferrara screening programme, ASC-US results are triaged with HPV DNA testing (HPV Cobas 4800 for types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 (Roche Diagnostics GmbH, Mannheim, Germany)), and women are considered as negative for intraepithelial lesion or malignancy (NILM) when HPV DNA-negative, while they are considered as LSIL when HPV DNA-positive. Therefore, abnormal cytology results in this study were all HPV+ ASC-US, AGC, ASC-H, LSIL, and HSIL results, with HPV+ ASC-US and LSIL considered as low-grade, and HSIL, ASC-H, and AGC as high-grade. For women with multiple tests during the study period, we considered only the first positive cytology result.

Exposed women were those who received at least one dose of HPV vaccine (out of the standard, recommended three doses) before the cytology result used for the analysis (the first positive one for women with at least one abnormal cytology, or the last negative for women with only NILM results).

**Statistical analysis.** The primary analyses consisted of four logistic regression models that were built to evaluate the potential association between abnormal cytology and one, two, three or at least one dose of HPV vaccine. Each model was adjusted for the following covariates (all included a priori): age (year of birth), residential area (city territory or province), country of birth (Italy or abroad), LBC test kit used (SurePath or ThinPrep), number of cytology tests until the test used for outcome assignment (censoring thereafter since women undergo further follow-up testing after a positive test).

As sensitivity analyses, all primary models were repeated stratifying by outcome (low- and high-grade cytology), birth cohort (1986–1989 and 1990–1993), and vaccine type (bivalent or quadrivalent). Analyses were repeated excluding women whose time from the first dose of vaccine to screening was shorter than three putative (buffer) periods of one month, six months and one year (chosen according to the uncertainty of the timing of immune response to vaccination and lesion

development after infection).[16, 17] Finally, the analyses were repeated using the total dose number (at the end of the study period) instead of the number of doses received before the screening test used for outcome assignment.[18] This was done to minimize the bias towards reducing the apparent effectiveness of one or two doses, since earlier screening tests are more likely to be impacted by infection prior to vaccination.[18, 19]

Survival analysis could not be used because, as most women only underwent one cytology test, a date for exposure start was not available for the whole sample, but a cumulative incidence curve was drawn to show the time trend of the positive cytologies. All analyses were carried out using Stata, version 15.1 (Stata Corp. College Station, Texas, 2018).

**Funding.** None was received.

**RESULTS**

**Cohort analysis.** Overall, in Ferrara Province, 11,773 resident women were born between 1986 and 1993.[15] Of them, 7,785 were screened (66.1%) (mean age 27.5 years, SD 2.3), of whom 391 were vaccinated (5.0% - Figure 1). From January 1st 2011 to December 27th 2018, all screened women were followed from the first to the last cytology screening test, with a mean follow-up of 1.5 years (range 0-7.5, as most women only underwent one test). As shown in Table S2, older birth cohorts had a higher screening uptake than younger ones, but a lower vaccination uptake: from 3.0% vaccine uptake among women born in 1986, to 8.6% among those born in 1993. The mean age at administration of the first vaccine dose decreased from 26.0 years in the 1986 cohort, to 18.9 years in the 1993 cohort, while the proportion of women who underwent two cytology tests also decreased from 30.9% in the 1986 cohort, to 0.1% in the 1993 cohort (Table S2).

A total of 893 women (11.5%) had at least one abnormal cytology. The proportion of positive tests was highest in the 1986 birth cohort (13.1%), progressively decreasing until the 1993 birth cohort (8.2% - Table 1). ThinPrep was used in the majority of tests considered for outcome assignment, and its results were less frequently positive (8.9%), than those of SurePath (25.0%) (a difference largely attributable to study design).

A lower proportion of abnormal cytology was observed among vaccinated (6.9%) compared to unvaccinated (11.7%) women ($p<0.01$), and this difference was substantial from the age of screening eligibility (Figure 2) or the date of first positive test (Figure S2). This trend was substantially

unchanged when the cumulative incidence curves were drawn for each birth cohort. The percentages of LSIL, ASC-H and HSIL were 6.4%, 0.5% and 0.0%, respectively, among vaccinated women, and 10.5%, 0.7% and 0.5%, respectively, among unvaccinated ones (Table S2).

**Odds ratios of abnormal cytology.** Multivariable analyses confirmed univariate results: women receiving at least one dose of vaccine were significantly less likely than unvaccinated women to have abnormal cytology (adjusted odds ratio - AOR: 0.52; 95% Confidence Interval - CI: 0.34 to 0.79 - Table 2). Similar results were obtained with a single dose of vaccine (AOR 0.52; 0.30 to 0.91), and restricting the analysis to the 1990–1993 birth cohorts (AOR: 0.47; 0.26-0.88). Probably due to the limited number of cases (n=90), the reduction in the risk of high-grade lesions for vaccinated women was not statistically significant (AOR: 0.57; 0.14 to 2.37 - Table S3).

The primary results were also confirmed in all secondary multivariable analyses, stratifying by one month, six months, and one year buffer periods (Table S4), vaccine type (Tables S5 and S6), and using the total dose number, as received at the end of the study period (Table S7).

## DISCUSSION

**Main Findings.** The main finding of the study is a large, significant reduction in the risk of abnormal cervical cytology in women receiving HPV vaccination. Vaccine effectiveness approached 50% in recipients of one or more vaccine doses, and remained consistent in all stratifications and sensitivity analyses, including different buffer periods and vaccine types, with the only exceptions being the analyses restricted to the first cohort (1986–1989, when vaccine uptake was very low), and to high-grade cytology (where the number of observations was too small).

**Strengths and Limitations.** While HPV type-specific prevalence in vaccinated populations was investigated in Italy,[20] this is the first evaluation of mid-term end-points of vaccine effectiveness. The strengths of the study include one of the highest screening uptakes, nationally and internationally,[21, 22] the use of deterministic linkage of vaccination and screening registries, minimizing the possibility of reporting, selection, and misclassification bias,[23] and the possibility to evaluate the impact of a single dose, due to the low vaccination completion rate. Clearly, low coverage is a limitation, that impaired the chances to assess vaccine effectiveness on less frequent, high-grade lesions. Additional limitations include the retrospective design, the relatively short follow-up, and the lack of data on sexual habits and smoking status.[24] Finally, as in all catch-up population studies, the generalizability of the results is limited, as HPV prevalence influences vaccine effectiveness.

**Interpretation.** These findings are consistent with the 52% fraction of abnormal cytology estimated to be caused by oncogenic HPV infection in Italian women aged 18–26 years old.[25] Also, the results are comparable with those reported in the systematic review of observational studies by Markowitz et al (2018).[26] Of the six studies reporting vaccination effectiveness,[27-32] two found that even a single dose was able to significantly reduce the rate of abnormal cytology. In these cases, one dose effectiveness was mostly attributed to the reduced transmission allowed by a high uptake of two and three doses,[28, 29] while similar results for a single dose reported in a recent Australian cohort study were deemed not entirely due to herd protection.[19] Likewise, in the present study the low overall uptake suggests that one vaccine dose may provide a fair level of protection. Beyond confirmation, our study is the first to document these findings in a context without school-based vaccination or active invitation to vaccination, where both the bivalent and quadrivalent vaccines were used. Vaccine efficacy reported from RCTs on samples of HPV-naïve girls, is higher, ranging from 90% to 100% against HPV types 16 and 18.[33, 34] This is presumably due to our inclusion of all abnormal cytology results (rather than only those linked to HPV 16 and 18), and to the late age at vaccination (mean 22.4 years) in this population. Indeed, a majority of the included women were already sexually active, and possibly infected with a vaccine-type HPV.[35] Therefore, a higher effectiveness may be hypothesized for primary target cohorts (vaccinated when 12-year old), who we will evaluate in future observational studies.

The 2015 Consensus Conference of the Italian Cervical Cancer Screening Group suggested expanding screening intervals and starting the screening at age 30-years instead of 25 for vaccinated women,[36] because the smaller rate of cervical abnormalities among the vaccinated clearly reduces the positive predictive value of cytology for precancerous lesions and cancer.[37] In line with previous findings, our results, particularly the absence of high grade cytology among the vaccinated, support the need to consider strategies in order to retain the effectiveness of screening.

In this study, the screening uptake increased with age, peaking at 77% for those aged 32-years, as the oldest women received up to three invitations for screening, versus one invitation for the youngest. In contrast, vaccination uptake was highest amongst younger women, probably due to a lower perceived benefit for older women at the start of the vaccination campaign.[38] Also, cohorts 1986-1989 were not eligible for co-payment, and obtained a significantly lower vaccine uptake (3.7%, n=166), than eligible cohorts 1990-1993 (uptake 6.8%, n=225), $p<0.001$. Therefore, the payment likely represented a barrier to vaccination.[39] Overall, the vaccination uptake (5.0%) was distant from

the 50%–80% obtained in Italian regions that actively offered catch-up immunizations, probably due to the absence of an active invitation.[40] Most of the positive screens were observed in women aged 25 and 28 years, those of screening rounds, and older cohorts had higher proportions of positive screens than younger ones, likely due to the longer period of screening. Since we used the first abnormal cytology for analyses, the test kit employed in the first part of the study (SurePath) found a higher proportion of positive results compared to ThinPrep, used from December 2015.

Some studies in the USA reported a strong, significant association between screening participation and HPV vaccination,[41] increasing the concern for unscreened women, who are also more likely to miss vaccination, thus carrying the highest risk for cancer.[42, 43] Unfortunately, no similar data were available in Italy. In this sample, no association between vaccination and screening was observed: vaccination uptake was 5.0% (n=391) among screened women, and 4.9% (n=193) among the unscreened women (p=0.7). However, only a small proportion of women were vaccinated, and thus results must be considered preliminary.

**CONCLUSION**

In the context of an organised cervical screening programme, the women who received one or more doses of HPV vaccination showed a halving of risk of cytological abnormalities. The protective role of HPV vaccination was confirmed for one dose, both vaccine types, and different buffer periods. In line with previous recommendations, screening intervals for vaccinated women should be widened.

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**Disclosure of Interests:** KC is co-PI and JMLB is a CI of an unrelated investigator-initiated trial of cervical cytology and primary HPV screening in Australia (‘Compass’), which is conducted and funded by the VCS Foundation, a government funded health promotion charity. The VCS Foundation have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. JMLB has never received direct funding or personal financial benefit from industry. Neither KC nor her institution on her behalf (Cancer Council NSW) receives direct funding from industry for this or any other project. The remaining authors have no disclosures. Completed

disclosure of interest forms are available to view online as supporting information.

**Contribution to Authorship:** CAM wrote the first and subsequent drafts of the manuscript with support from SN, LM, DY, and PU. CP and AC extracted the data. CAM cleaned the data and did the analysis, with support from JB, KC, LM, and ADT. SN, DY, PU, JB, KC, LM, MP, PGR, ES, MH, and KS provided critical revisions to the manuscript. All authors approved the final draft.

**Details of Ethics Approval:** Ethics approval for this study was granted by the ethics committee of the Central Emilia Area, Italy, authorization number 365/2019/Oss/AUSLFe, on July 17th 2019. Consent to participate was not necessary because only data routinely gathered for clinical purposes was retrospectively collected. The study was performed in accordance with the Declaration of Helsinki.

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**Table 1: Demographic characteristics, test kit type, number of cytology screens, receipt of vaccine doses, and vaccine type of women with and without an abnormal LBC result in Ferrara, Italy, screening 2011-2018.**

| Characteristics | Total sample, n=7,785 N | Abnormal cytology, n=893 % (N) | Low-grade, n=803 % | High-grade, n=90 % |
|---|---|---|---|---|
| *Birth cohort* | | | | |
| 1993 | 662 | 8.2 (54) | 7.6 | 0.7 |
| 1992 | 793 | 10.2 (81) | 9.5 | 0.8 |
| 1991 | 863 | 11.4 (98) | 10.9 | 0.5 |
| 1990 | 990 | 11.9 (118) | 10.9 | 1.3 |
| 1989 | 1,047 | 11.4 (119) | 10.3 | 1.4 |
| 1988 | 1,104 | 11.7 (129) | 10.4 | 1.6 |
| 1987 | 1,090 | 12.1 (132) | 11.1 | 1.2 |
| 1986 | 1,236 | 13.1 (162) | 11.4 | 2.2 |
| *Residential area* | | | | |
| Ferrara city | 2,632 | 12.5 (328) | 11.3 | 1.5 |
| Province | 5,153 | 11.0 (565) | 10.0 | 1.2 |
| *Country of birth* | | | | |
| Italy | 6,076 | 12.1 (735) | 11.3 | 1.0 |
| Abroad | 1,709 | 9.3 (158) | 7.2 | 2.3 |

| | | | | |
|---|---|---|---|---|
| *Test kit* | | | | |
| SurePath[A] | 1,241 | 25.0 (310) | 23.1 | 3.1 |
| ThinPrep | 6,544 | 8.9 (583) | 8.1 | 1.0 |
| *No. of cytology screens[B]* | | | | |
| 1 | 5,921 | 8.1 (478) | 7.4 | 0.8 |
| >1 | 1,864 | 22.3 (415) | 20.2 | 3.2 |
| *Vaccination dose* | | | | |
| 0 | 7,394 | 11.7 (866) | 10.7 | 1.3 |
| ≥1 | 391 | 6.9 (27) | 6.4 | 0.5 |
| 1 | 212 | 7.1 (15) | 6.2 | 1.0 |
| 2 | 83 | 9.6 (8) | 9.6 | 0.0 |
| 3 | 96 | 4.2 (4) | 4.2 | 0.0 |
| *Vaccine type* | | | | |
| Bivalent | 278 | 7.9 (22) | 7.3 | 0.8 |
| Quadrivalent | 113 | 4.4 (5) | 4.4 | 0.0 |

Low-grade= includes HPV+ ASC-US (HPV DNA-positive atypical squamous cells of undetermined significance), and LSIL (low-grade squamous intraepithelial lesion). High-grade= includes HSIL (high-grade squamous intraepithelial lesion), ASC-H (high-grade atypical squamous cells) and AGC (atypical glandular cells). [A] The SurePath test kit was replaced by ThinPrep in December 2015. [B] Number of LBCs until the first abnormality detected (censoring afterwards), and until the last negative test for negative women.

**Table 2. Odds ratios (95% confidence interval) of cervical abnormalities for all cohorts and cohorts 1986 to 1989 and 1990 to 1993, by dose number.**

| Dose | All cohorts, OR (95% CI) (n=7,785) | All cohorts, AOR (95% CI) (n=7,785) | Cohorts 1986–1989, AOR (95% CI) (n=4,477) | Cohorts 1990–1993, AOR (95% CI) (n=3,308) |
|---|---|---|---|---|
| 0 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1 | 0.57 (0.34-0.97)* | 0.52 (0.30-0.91)* | 0.61 (0.29-1.29) | 0.43 (0.17-1.05) |
| 2 | 0.80 (0.39-1.67) | 0.61 (0.28-1.37) | 0.75 (0.26-2.12) | 0.65 (0.20-2.16) |
| 3 | 0.33 (0.12-0.89)* | 0.40 (0.15-1.11) | 0.33 (0.04-2.49) | 0.44 (0.14-1.43) |
| ≥ 1 | 0.56 (0.38-0.83)** | 0.52 (0.34-0.79)** | 0.61 (0.34-1.09) | 0.47 (0.26-0.88)* |

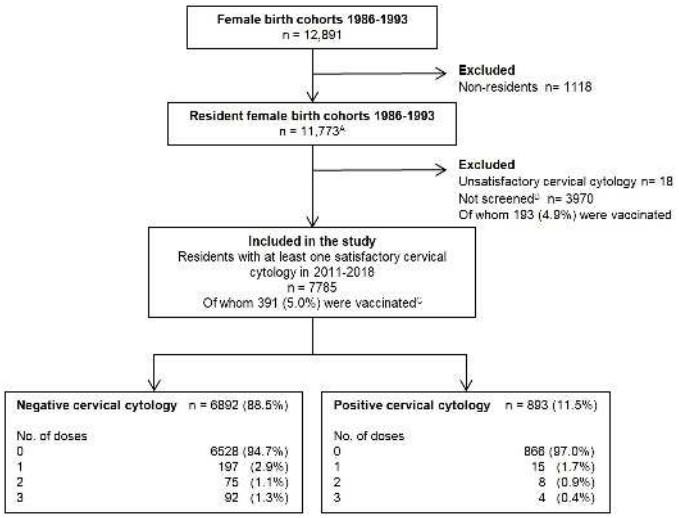
OR= unadjusted odds ratios from logistic regression. AOR= adjusted odds ratios from logistic regression adjusted for year of birth, being born abroad, residential area, number of screens, and test kit. * $p<0.05$. ** $p<0.01$.

**FIGURE LEGENDS**

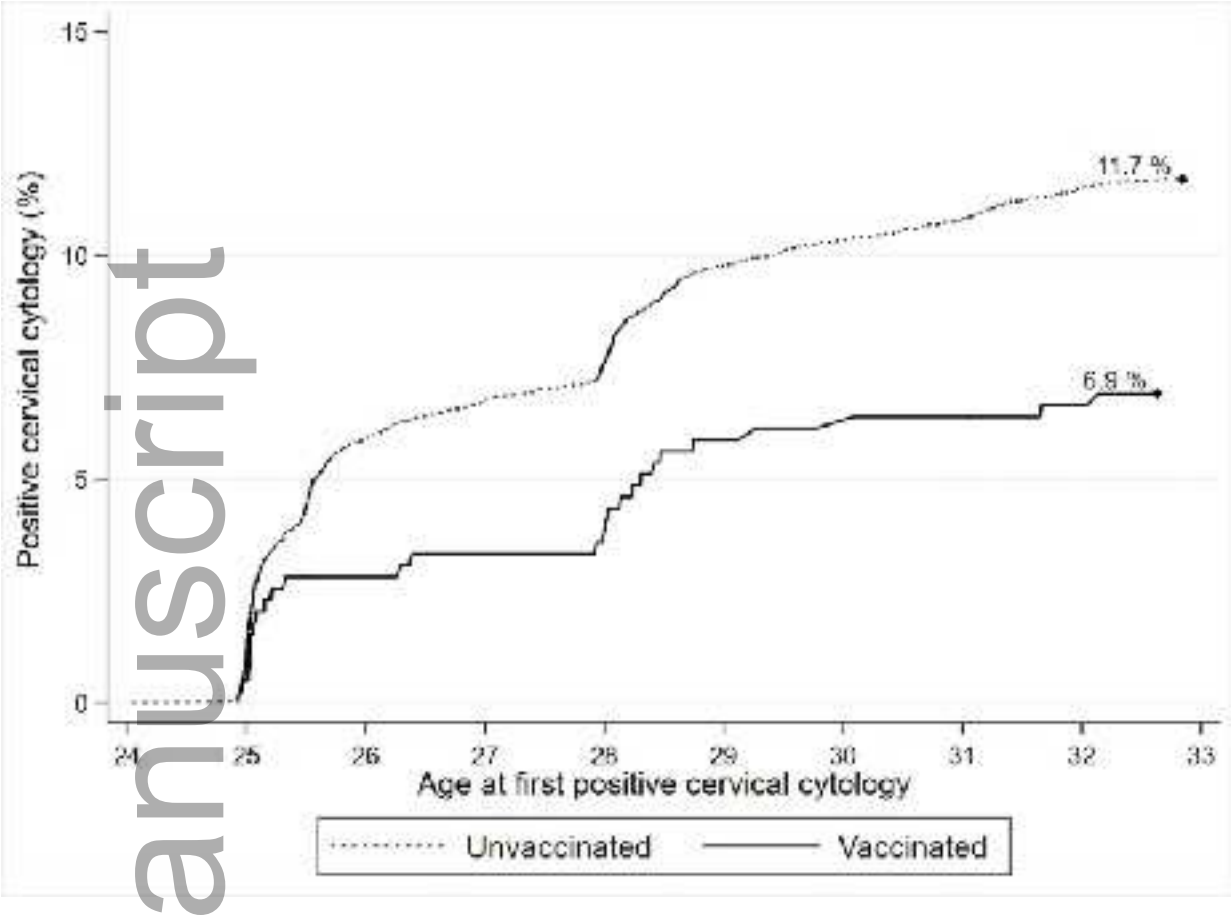
**Figure 1. Flow diagram of population selection.**

[A] Resident population on January 1st 2018.[15] [B] Number of not screened was obtained by subtracting the final sample of 7785 resident women, and the 18 with unsatisfactory cervical cytology, from the 11,773 resident women. [C] Vaccinated before the cytology test used for outcome assignment (13 women who were vaccinated after it, three of whom had at least one positive screen, and the rest with only negative tests, were considered unvaccinated).

**Figure 2. Cumulative incidence curve of abnormal cervical cytology by age and vaccination status.**




bjo_16429_f1.jpg




bjo_16429_f2.jpg

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