**Human Papillomavirus prevalence in Senegalese women in relation with age**

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**Abstract**

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**Background:** Senegal has high cervical cancer incident rates of 34.7 per 100,000 women-years, disproportionately affecting women at different ages. Data on age-specific HPV prevalence, which potentially could have implications on cervical cancer screening and prevention, for Senegal are scant. Therefore, this study primarily sought to determine the age-specific HPV prevalence, overall and by HPV type, as well as the risk factors for HPV positivity in older women, among women in Senegal.

**Methods:** This cross-sectional study included women aged 15-84 years undergoing screening in outpatient clinics in Dakar, Senegal, between 2002-2010. The sociodemographic and reproductive data, sexual behavior, and HPV genotype results were analyzed using R software. The Chi-square test was used to compare HPV prevalence across age groups and demographic and reproductive characteristics. Logistic regression was used to calculate odds ratios (OR) and to determine predictors for HPV.

**Results:** A total of 2,031 women (mean age 43.7 years) were included. Overall HPV prevalence was 28.9% among the study population. HPV prevalence showed a bimodal age distribution

among women differing by 5 years, with the first peak at the 25-29 ages (34.0%) and the second peak among >55 years old women (47.6%). The bivariate association of HPV with a priory selected risk factors showed a significant association with the age groups, relationship status, lifetime number of sex partners and contraception use. The most common high risk HPV types (hrHPV) were nonavalent vaccine-types HPV 16 (2.6%), HPV 58 (3.3%), HPV 52 (2.6%), HPV 33 (2.2%) and HPV 31 (2.0%). Women aged 55-84 had a higher prevalence of any HPV (37.0%) and multiple HPV infections (13.5%) and a lower prevalence of hrHPV infections (9.0%) than younger women.

**Conclusions:** Recognizing the increased HPV prevalence among older, for whom periodic cervical screening may not be feasible, is essential in terms of its influence on the cervical screening programs. Revising the age of women for the cervical screening programs and screening intervals may help prevent women at older ages with persistent hrHPV infections from developing cervical cancer.

## I. INTRODUCTION

HPV is the etiological factor in benign cutaneous warts, juvenile respiratory papillomatosis, as well as squamous intraepithelial lesions, and is associated with cervical, anogenital and head and neck cancers (Burd & Dean, 2016; Michael Loeffelholz (Editor-in-Chief) et al., 2016; Shanmugasundaram & You, 2017) . In the majority of infected individuals, HPV infection is cleared by the immune system within 12-18 months of primary infection (Sadate-Ngatchou et al., 2016); however, the viral infection can continue to persist latently in a subset of the population, and 10–15% of women do not clear HPV infection (Groves & Coleman, 2015; Michael Loeffelholz (Editor-in-Chief) et al., 2016). Individuals with persistent HPV infection have an increased chance of the development of precancerous lesions and subsequently develop cancers at the site of infection (Shanmugasundaram & You, 2017; Whitham et al., 2017). The time from HPV infection to cervical cancer development is typically 20 years; therefore, rapid progression of cervical cancers in non-immunocompromised women rarely occurs (Rodriguez et al., 2008).

Based on their oncogenic potential, HPV can be subdivided into low-risk and high-risk types (Burd & Dean, 2016; Groves & Coleman, 2015). High-risk HPVs that are most frequently associated with malignant genital cancers include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. HPV 16 and HPV 18 are responsible for roughly 70% of cervical cancer cases (Burd & Dean, 2016; Shanmugasundaram & You, 2017; Whitham et al., 2017).

The prevention strategies for cervical cancer include vaccination against HPV as primary prevention and cervical screening by Pap smear, increasingly in conjunction with HPV-DNA testing as secondary prevention. Out of currently available three vaccines, as of 2017, Gardasil 9 (protects against HPV 6,11,16,18,31,33,45,52,58) is the only HPV vaccine available for use in the United States, although Gardasil (HPV 6,11,16,18) and Cervarix (HPV 16,18) continue to be used worldwide (Bedell et al., 2020; Dilley et al., 2020). As an HPV screening strategy, WHO

suggests using HPV DNA detection as the primary screening test with screening priority to be given to women aged 30–49 years and with a 5 to 10 year screening interval (World Health Organization 2021).

***Cervical cancer burden in Africa***

Cervical cancer is the fourth most frequently occurring malignancy in women worldwide, with an estimated 570,000 new cases and 311,000 deaths in 2018 (Arbyn et al., 2020). Approximately 85% of the worldwide deaths from cervical cancer occur in lower middle-income countries (LMIC), and the death rate is 18 times higher in LMICs compared with wealthier countries (Hull et al., 2020). In Africa, cervical cancer is the most common cancer in women with about 117,316 new cases annually, ranking as the second leading cause of female cancer (Bruni L et al., 2021). The high incidence of cervical cancer is a consequence of the lack of organized screening and HPV vaccination programs. Only nine West African countries have introduced a pilot HPV vaccination program and currently, Senegal and Gambia are the only West African countries with a national HPV immunization program (Wilson, 2021).

Coverage of cervical cancer screening in LMICs is on average 19% compared to 63% in developed countries (Gakidou et al., 2008). Although well-organized cervical screening programs are proven to reduce cervical cancer incidence and mortality (Bruni L et al., 2021) , factors like knowledge about the cervical cancer, education level, age, awareness of place of screening influence screening uptake in Africa (Habtu et al., 2017; Orang'o et al., 2016; Yimer et al., 2021). In addition, cervical cancer screening methods vary between countries. The most frequently used methods is cytology with HPV-DNA is being an alternative (Bruni L et al., 2021). Visual inspection with acetic acid (VIA) is employed as an alternative cost-effective screening strategy (Anaman-Torgbor et al., 2020; Bruni L et al., 2021; Fitzpatrick et al., 2019).

In Senegal, women are diagnosed with cervical cancer every year with a standardized incidence rate of cervical cancer of 34.7 per 100,000 women-years (Fall et al., 2019). Gavi-supported successful pilot demonstration project of HPV vaccination led to the nationwide introduction of the HPV vaccine in 2018. Quadrivalent HPV vaccine has been administered to 9-year-old girls with a 6-month minimum interval between the two doses, using a routine service delivery strategy at health facilities, schools, and other outreach sites. However, the vaccine implementation in Senegal was followed by a global HPV vaccine shortage, vaccine hesitancy by locals, and resistance of teachers and parents against vaccine introduction in the community (Casey et al., 2022). There is no population-based cervical screening program in Senegal. Some evidence-based screening programs are associated with a low participation rate, with 6.9% of women aged 18-69 (Diouf et al., 2020). The participation rate is especially low in rural areas and in older age groups (1.9% of women aged 40–49 years and 0% of women aged ≥50 years) (Diouf et al., 2020; Dykens et al., 2017; Xi et al., 2003). Only three rural regions of Senegal have started cervical screening programs providing limited services to 32.5% of rural residents between the ages of 30 and 59 years (Dykens et al., 2017; Haque et al., 2020). Evidence-based screening programs used the visual inspection method (VIA) as a cervical screening method in Senegal (Dykens et al., 2017; Gabrielli et al., 2018).

***Age-specific HPV prevalence***

HPV is transmitted by almost all forms of sexual contact including penetrative intercourse, oral sex, genital contact, and genital skin-to-skin contact (Michael Loeffelholz (Editor-in-Chief) et al., 2016). This feature makes the virus common among young sexually active women. The reported highest HPV prevalence in North America was among females aged 20-24, in Central and South America among 14-24 years old women, in Asia in 22-36 years old women, and in Europe among women in their early 20s (Smith et al., 2008). In Africa, age-specific HPV prevalence showed different prevalence trends. In Tunisia, Kenya, Uganda and Zimbabwe,

HPV-DNA prevalence was highest in young women and decreased steadily with age (Smith et al., 2008). In Nigeria and Mozambique, HPV positivity also declined with age but generally reached a plateau at approximately 40 years of age (Smith et al., 2008). HPV positivity increased slightly in older-aged women in Senegal (over 55 years of age) and in Nigeria (over 50 years of age) (Clarke et al., 2011; Gage et al., 2012; Xi et al., 2003). Women surveyed in the Gambia seemed to have a relatively constant prevalence of HPV infection among those aged 15 to 54 years (Awua et al., 2017; Smith et al., 2008) and in Guinea HPV prevalence was constant across all age groups (Keita et al., 2009).

***Rationale for the study***

In order to prevent cervical cancer in limited resource areas, it is crucial to assess the impact of standard screening recommendation ages and intervals between screening ages. Learning more about age-specific HPV prevalence will help inform the timing of HPV screening efforts in limited-resource settings where the WHO recommended 5 to10 year interval period for period for screening may not be feasible. Recognition of increased HPV prevalence among older women who are left out of the screening and vaccination programs has the potential to inform new screening approaches with a focus on older women. Identification of age-specific HPV prevalence and HPV types across different age groups would provide an understanding of the epidemiology of HPV infection and thus, clarify how screening might be optimized to fit the observed epidemiologic patterns. It may also inform recommended ages for HPV vaccination in certain populations in low-resource countries.

The intention of this study was to investigate the association between age and HPV prevalence in women of all ages in Senegal. The specific objectives were defining the HPV prevalence for women in different age groups, variation in HPV types among HPV-positive women differing by age group (5-year intervals), and identification of risk factors for HPV detection for older women (>55 years).

## II. MATERIALS AND METHODS

### *Study population*

This is a secondary analysis of data from two prospective studies conducted in Senegal, West Africa, aimed to 1) identify biomarkers for HPV-related disease progression, DNA hyper-methylation in cervical cancer, 2005-2010) develop new approaches for cervical cancer control, 2002-2007. These subjects have been previously described in the literature (Feng et al., 2005; Hanisch et al., 2013; Heitzinger et al., 2012; Whitham et al., 2017), although for the current study, we excluded women with HIV infection (n=643).

### *Data collection*

Procedures for data and sample collection have been previously described (Feng et al., 2005; Whitham et al., 2017). Briefly, women older than 15 years were recruited from an outpatient primary care clinic (Pikine) and an outpatient infectious disease clinic (SMIT, CHNU de Fann) in Dakar. Upon enrollment, participants provided written informed consent. A questionnaire was administered to obtain information on the sociodemographic characteristics, sexual behavior, sexual and reproductive history, use of contraception and history of sexually transmitted infections. Gynecologic examinations were conducted, and cervical swab samples were obtained for HPV detection.

Testing for HPV detection was conducted as described by Feng et al. (Feng et al., 2009). Specimens were tested for HPV DNA with a polymerase-chain-reaction (PCR) assay using MY09 and MY11 L1 consensus primers. HPV DNA was extracted using QIAamp DNA blood mini kit according to the manufacturer's protocol (Qiagen, Valencia, CA). Due to the differences between studies, for some samples, a non-kit-based isolation technique was used: extraction was performed with 20 µg/ml proteinase K at 37°C for 1 h, and genomic DNA was ethanol

precipitated from 200 µl of the processed samples. The quality and integrity of sample DNA for polymerase chain reaction (PCR) was verified by amplification of a 268 base pair region of the human b-globin gene.

The presence of HPV DNA was determined by PCR amplification followed by dot blot hybridization for all samples, and positive samples were subsequently genotyped for type-specific HPV. The vast majority of samples were tested using the Roche Linear array assay (2000–2005) or a liquid bead microarray assay (2005–2010), which detected 38 types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and 84, additional HPV types of 61, 62, 64, 67, 69, 70, 71, 72, 81, IS39 (a subtype of HPV 82), and CP6108 (also known as HPV 89). Due to the differences between studies, some samples were genotyped using the Roche line blot, which detected 27 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and 84). Samples positive by PCR amplification but not positive for any of the type specific assays were classified as positive, untyped.

***Statistical methods***

Data was analyzed using R software version 4.1.0. We evaluated the association between age and HPV positivity to indicate a difference in HPV prevalence across age groups (5 years intervals). The Chi-square test and, where appropriate, Fisher's exact test were used to compare HPV prevalence across age groups and demographic and reproductive characteristics. We evaluated the potential risk factors that might be associated with women at older ages, 55 years and older.

Potential confounding factors were chosen *a priori* and included age, lifetime sex partners, relationship status, number of cowives in those in polygamous marriages, number of children, and use of contraception. Age was categorized (15-29, 30-54, and 55-84 years) in order to

compare the older women with the lowest-risk HPV group (mid-aged women). Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression to estimate predictors for HPV (univariate model). Age categories and the variables associated with HPV positivity were included in the multivariable model to identify independent predictors of HPV. A level of 0.05 was chosen to indicate statistical significance.

HPV DNA types were classified according to their oncogenic potential, with HPV types 16, 18, 31, 33, 35, 39, IS39, 45, 51, 52, 56, 58, 59, 66 and 68 classified as high-risk types (National Cancer Institute, 2021). The distribution of high-risk and low-risk HPV types and multiple infections were determined for younger, middle-aged, and older women.

## III. RESULTS

The complete demographic, behavioral and cervical sample-related data were extracted for a total of 2,031 subjects, 1,773 women from the "DNA hypermethylation in cervical cancer" study and 258 women from the "Developing new approaches for cervical cancer control" study.

The mean age of all individuals was 43.7, with a minimum age of 15 and a maximum of 84 years (Table 1). The majority of subjects (98.7%) were Senegal-born women. The study subjects belonged to different ethnicities, Wolof – 61.4%, Pulaar – 15.5%, Serere – 10.9%, Sarakhole – 1.0%, Mandjack – 1.8%, Diola – 2.9%, and 6.4% to others. Almost half of the women (53.0%) had no formal education, whereas 30.6% had completed primary schooling and 14.3% had secondary schooling. Only 2.2% of studied subjects had a university degree. Nine percent of women had no children, 55.3% had one to five children and 36% had more than six children. Three percent of women were single, the majority of the women were in monogamous or polygamous marriage relationships, 41.1% and 42.1%, respectively, and 13.7% were separated or widowed.

**Table 1. Baseline characteristics of women in Senegal, West Africa, 2002-2010**

| | Hypermethylation (N=1773) | New Approaches (N=258) | Overall (N=2031) |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) | 44.4 (9.84) | 39.0 (11.9) | 43.7 (10.3) |
| Median [min, max] | 45.0 [18.0, 84.0] | 39.0 [15.0, 82.0] | 44.0 [15.0, 84.0] |
| **Birthplace** [a] | | | |
| Senegal | 1746 | 17 | 1763 (98.7) |
| Guinea-Bissau | 10 | 0 | 10 (0.6) |
| Gambia | 3 | 0 | 3 (0.2) |
| Mauritania | 2 | 0 | 2 (0.1) |
| Mali | 2 | 1 | 3 (0.2) |
| Other West Africa | 2 | 0 | 2 (0.1) |
| Central Africa | 3 | 0 | 3 (0.2) |
| Other | 1 | 0 | 1 (0.1) |
| **Ethnicity** [b] | | | |
| Wolof | 1144 | 99 | 1243 (61.4) |
| Pulaar | 261 | 54 | 315 (15.5) |
| Serere | 189 | 32 | 221 (10.9) |
| Sarakhole | 15 | 6 | 21 (1.0) |
| Mandjack | 31 | 6 | 37 (1.8) |
| Diola | 38 | 21 | 59 (2.9) |
| Other | 94 | 36 | 130 (6.4) |

| | | | |
|---|---|---|---|
| **Education** [c] | | | |
| None | 950 | 116 | 1066 (53.0) |
| Primary | 550 | 67 | 617 (30.6) |
| Secondary | 241 | 48 | 289 (14.3) |
| University | 22 | 23 | 45 (2.2) |
| **Lifetime sex partners** [d] | | | |
| 1 | 1161 | 129 | 1290 (64.7) |
| 2-5 | 565 | 113 | 678 (34.0) |
| 6 and more | 17 | 7 | 24 (1.7) |
| **Marital status** [e] | | | |
| Single | 25 | 35 | 60 (3.0) |
| Monogamous marriage | 724 | 93 | 817 (41.1) |
| Polygamous marriage 1 cowife | 484 | 41 | 525 (26.4) |
| Polygamous marriage >1 cowives | 283 | 28 | 311 (15.7) |
| Separated | 112 | 32 | 144 (7.2) |
| Widowed | 111 | 19 | 130 (6.5) |
| **Number of children** [f] | | | |
| No children | 127 | 49 | 176 (8.7) |
| 1-5 | 973 | 144 | 1117 (55.3) |
| 6-10 | 638 | 57 | 695 (34.4) |
| >11 | 29 | 3 | 32 (1.6) |

*Notes:*

[a] *Birthplace information was missing for 244 women; numbers may not add up to the total due to missing data.*

[b] *Five women did not have ethnicity information; numbers may not add up to the total due to missing data.*

[c] *Fourteen women were with unknown educational status; numbers may not add up to the total due to missing data.*

[d] *Number of Lifetime sex partners was missing for the 39 women; numbers may not add up to the total due to missing data.*

[e] *Marital status combined with a number of cowives was not available for the 44 women; numbers may not add up to the total due to missing data.*

[f] *Number of children was not included for the 11 women; numbers may not add up to the total due to missing data.*

HPV DNA was detected in 587 subjects (Table 2). Overall HPV prevalence was 28.9% for the study population.

**Table 2.** HPV prevalence by baseline characteristics among women in Senegal, West Africa, 2002-2010

| **Variables** | **Number** positive/total | **HPV prevalence** **%** |
|---|---|---|
| ***Overall*** | 587/2031 | 28.9 |

| | | |
|---|---|---|
| ***Age groups*** | | |
| 15-24 | 23/82 | 28.0 |
| 25-29 | 28/83 | 34.0 |
| 30-34 | 54/216 | 25.0 |
| 35-39 | 71/287 | 25.0 |
| 40-44 | 110/364 | 30.2 |
| 45-49 | 112/414 | 27.0 |
| 50-54 | 82/296 | 27.7 |
| 55-59 | 53/166 | 32.0 |
| 60-64 | 34/81 | 42.0 |
| 65-84 | 20/42 | 47.6 |
| | | p-value = 0.01 |
| ***Education*** | | |
| none | 296/1066 | 27.8 |
| primary | 184/617 | 29.8 |
| secondary | 86/289 | 29.8 |
| university | 17/45 | 37.8 |
| | | p-value = 0.43 |
| **Relationship status** | | |
| single | 27/60 | 45.0 |
| monogamous | 191/817 | 23.3 |
| polygamous - 1 cowife | 156/525 | 29.7 |
| polygamous >1 cowives | 97/311 | 31.2 |
| separated | 55/144 | 38.2 |

| | | |
|---|---|---|
| widowed | 46/130 | 35.4 |
| | | p-value <0.001 |
| ***Number of sex partners*** | | |
| one | 312/1290 | 24.1 |
| two to five | 250/678 | 36.9 |
| six and more | 11/24 | 45.8 |
| | | p-value<0.001 |
| ***Contraception use**** | | |
| none | 495/1662 | 29.8 |
| condoms | 12/28 | 42.9 |
| hormonal | 58/265 | 21.9 |
| others | 21/68 | 30.9 |
| | | p-value = 0.02 |

The pattern of HPV prevalence by age group is shown in Table 2 and Figure 1. HPV prevalence was 28.0% among the 15-24 age group and reached a peak of 34.0% among women in the 25-29 ages. Middle-age groups, women 30-54 years old, showed relatively stable low HPV prevalence varying from 25% to 30.2%. The highest HPV prevalence was observed among age groups of 60-64 and women older than 65, 42.0% and 47.6%, respectively.

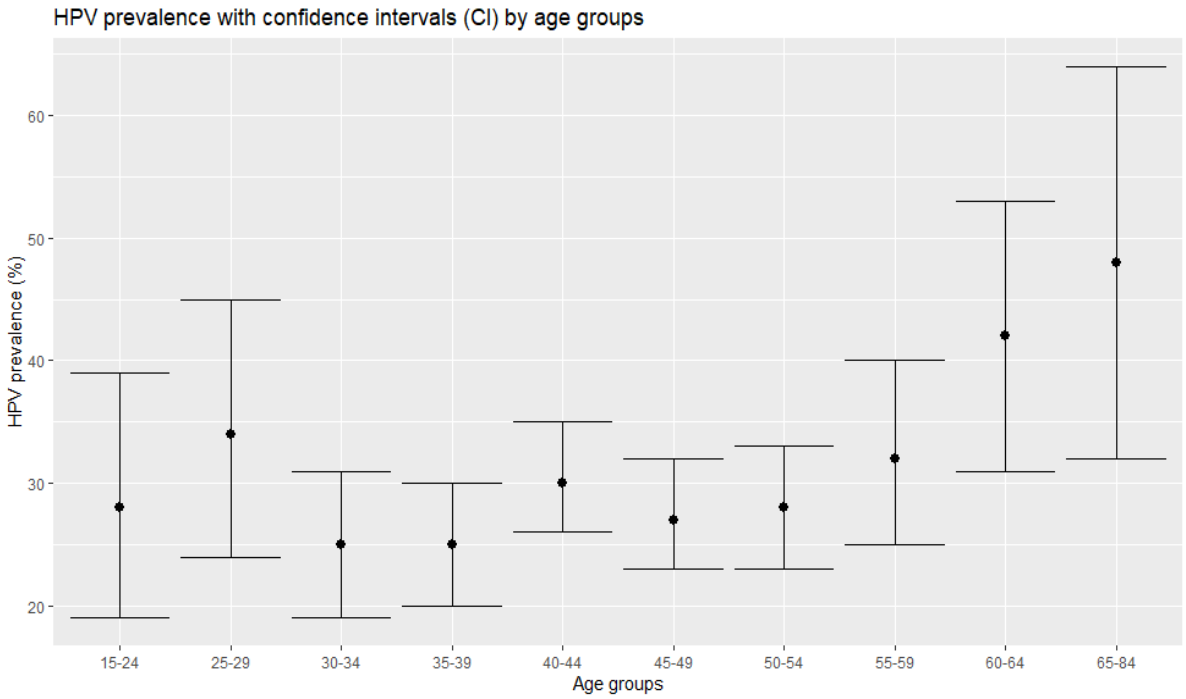



**Fig 1. HPV prevalence by age group, Senegal, West Africa, 2002-2010**

We estimated the bivariate association of HPV with baseline characteristics of the studied women. HPV prevalence was significantly associated with the age groups ($\chi2=17.8$, $p = 0.001$), relationship status ($\chi2=29.4$, $p<0.001$), lifetime number of sex partners ($\chi2=38.3$, $p <0.001$), and contraception use ($\chi2=7.6$, $p = 0.02$). However, the education status of women was not associated with HPV prevalence ($\chi2=2.7$, $p = 0.43$) (Table 2).

Table 3 presents a) the association between age and HPV positivity and b) a multivariate model exploring the association of age and HPV positivity adjusted for relationship status, lifetime sex partners, contraception use, cowives, education status, and the number of children. In crude analysis, older women aged 55 and above were more likely to be infected with HPV (OR=1.57, 95% CI 1.21-2.05) than middle-aged women ages 30-54. After adjusting for confounders, age (>

55), the lifetime sex partners and marital status were still significantly associated with HPV positivity (age group 55-84: OR = 1.43, 95% CI 1.06-1.92). Other factors associated with HPV positivity included having multiple lifetime sex partners (OR = 1.62, 95% CI 1.31-2.01), and have a classification of separated marital status (OR = 1.62, 95% CI 1.08-2.42).

**Table 3.** Factors associated with the HPV positivity in women, Senegal, West Africa, 2002-2010. Unadjusted and adjusted odds ratios

| ***Variables*** | **Crude OR (95% CI)** | **Adjusted OR* (95% CI)** |
|---|---|---|
| **Age groups in years** | | |
| 15-29 | 1 20 (0.84, 1.70) | 1.22 (0.81, 1.84) |
| 30-54 | *Ref* | *Ref* |
| 55-84 | **1.57 (1.21,2.05)** | **1.43 (1.06, 1.92)** |
| **Lifetime sex partners** | | |
| one partner | *Ref* | *Ref* |
| **t**wo and more partners | **1.86 (1.52, 2.26)** | **1.62 (1.31, 2.01)** |
| **Number of children** | | |
| no children | *Ref* | *Ref* |
| 1-5 | 0.66 (0.47, 0.92) | 0.80 (0.55, 1.17) |
| six and more | 0.75 (0.53, 1.06) | 0.90 (0.59, 1.35) |
| **Contraception** | | |
| None | **1.51 (1.11, 2.06)** | 1.15 (0.83, 1.60) |

| | | |
|---|---|---|
| condom | **2.68 (1.20, 5.98)** | 1.51 (0.54, 4.28) |
| hormonal | *Ref* | *Ref* |
| other | 1.60 (0.88, 2.88) | 1.38 (0.75, 2.55) |
| **Relationship status** | | |
| Single | **2.68 (1.57, 4.57)** | 1.86 (0.91, 3.78) |
| monogamous marriage | *Ref* | *Ref* |
| polygamous marriage & 1 cowife | **1.39 (1.08, 1.77)** | 1.27 (0.98, 1.64) |
| polygamous marriage & >1 cowives | **1.49 (1.11, 1. 98)** | 1.25 (0.92, 1.70) |
| separated | **2.03 (1.39, 2.94)** | **1.62 (1.08, 2.42)** |
| widowed | **1.80 (1.21, 2.66)** | 1.36 (0.88, 2.11) |

Out of 587 HPV-positive cervical samples, HPV types were identified for 550. Of these, 342 (16.8%) were established to have at least one hrHPV and 372 (18.3%) had at least one lrHPV type (Table 4). Analysis of HPV type prevalence showed that the five most prevalent hrHPV types were nanovalent vaccine-types, including HPV 58 (3.3%), HPV 16 (2.6%), HPV 52 (2.6%), HPV 33 (2.2%) and HPV 31 (2.0%). Overall, 91.2% of hrHPV infections were nonavalent vaccine preventable. Among lrHPV types the highest prevalence was detected for HPV 54 (3.9%), HPV61 (3.5%), HPV 53 (3.0%), HPV 83 (2.8%) and HPV 62 (2.5%).

**Table 4.** Overall HPV prevalence for specific types, a) high-risk HPV types, b) low-risk HPV types, Senegal, West Africa, 2002-2010

**a) hrHPV types**

| | HPV type | Total number of subjects N = 2031 | Overall prevalence % |
|---|---|---|---|
| | **High-risk types** | **Subjects with at least one hrHPV n=342** | **16.8** |
| 1 | type 16 | 53 | **2.6** |
| 2 | type 18 | 34 | **1.7** |
| 3 | type 31 | 40 | **2.0** |
| 4 | type 33 | 45 | **2.2** |
| 5 | type 35 | 9 | **0.4** |
| 6 | type 39 | 14 | **0.7** |
| 7 | type IS39 | 10 | **0.5** |
| 8 | type 45 | 20 | **1.0** |
| 9 | type 51 | 32 | **1.6** |
| 10 | type 52 | 53 | **2.6** |
| 11 | type 56 | 20 | **1.0** |
| 12 | type 58 | 67 | **3.3** |
| 13 | type 59 | 24 | **1.2** |
| 14 | type 66 | 20 | **1.0** |
| 15 | type 68 | 23 | **1.1** |

**b) lrHPV types**

| | HPV type | Total number of subjects N = 2031 | Overall prevalence % |
|---|---|---|---|
| | **Low-risk HPV** | **Subjects with at least one lrHPV n=372** | **18.3** |
| 16 | type 6 | 16 | **0.8** |
| 17 | type 11 | 3 | **0.1** |
| 18 | type 26 | 1 | **0.0** |
| 19 | type 40 | 4 | **0.2** |
| 20 | type 42 | 12 | **0.6** |
| 21 | type 53 | 60 | **3.0** |
| 22 | type 54 | 79 | **3.9** |
| 23 | type 55 | 16 | **0.8** |
| 24 | type 57 | 0 | **0.0** |
| 25 | type 61 | 72 | **3.5** |
| 26 | type CP 6108 | 8 | **0.4** |
| 27 | type 62 | 50 | **2.5** |
| 28 | type 64 | 0 | **0.0** |
| 29 | type 67 | 4 | **0.2** |
| 30 | type 69 | 1 | **0.0** |
| 31 | type 70 | 21 | **1.0** |
| 32 | type 71 | 16 | **0.8** |
| 33 | type 72 | 11 | **0.5** |

| | | | |
|---|---|---|---|
| 34 | type 73 | 19 | **0.9** |
| 35 | type 81 | 44 | **2.2** |
| 36 | type 82 | 4 | **0.2** |
| 37 | type 83 | 57 | **2.8** |
| 38 | type 84 | 27 | **1.3** |

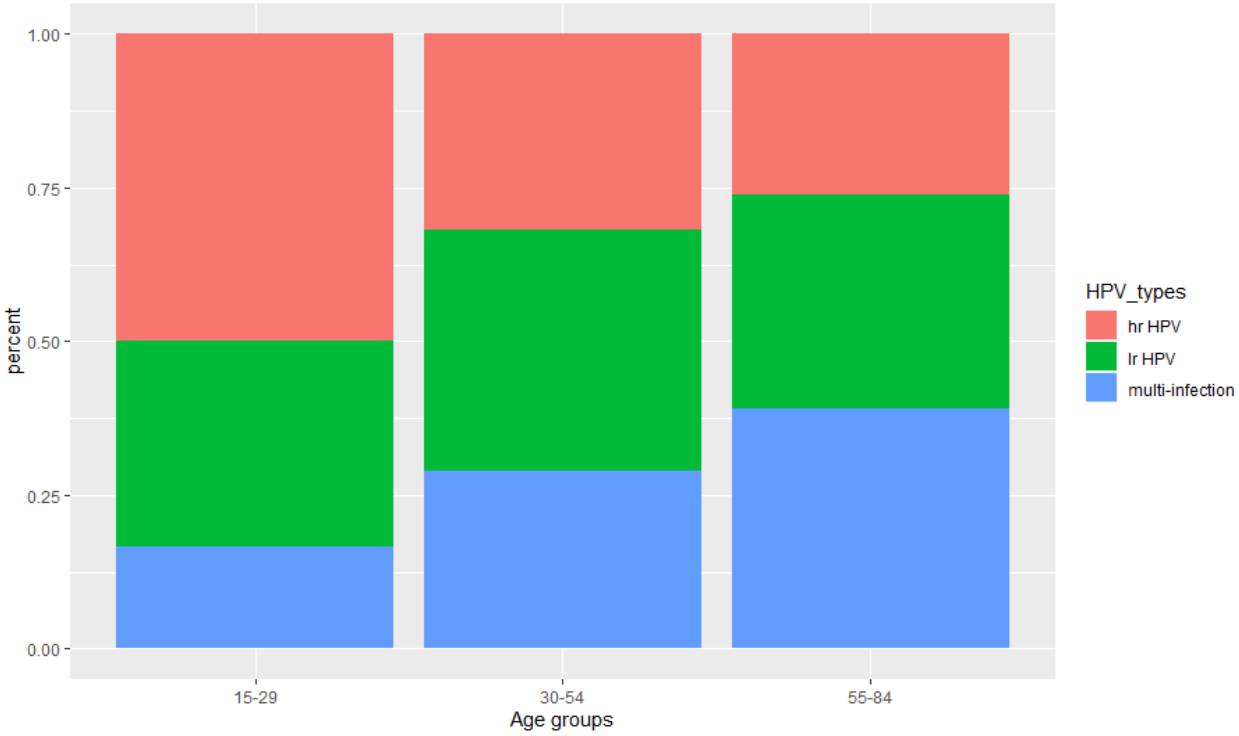
We also explored the distribution of high-risk and low-risk HPV types in 550 women by age categories (Table 5). Although the younger age category, 15-29, had higher hrHPV prevalence, women at 55-84 ages had a higher prevalence of any HPV and multiple HPV infections (Figure 2).

**Table 5.** Distribution of low-risk, high-risk, and multiple types by age group.

| Age Group | Any HPV* | only lrHPV type(s) n=208 | only hrHPV type(s) n=178 | Multiple HPV types (hr and lr types) |
|---|---|---|---|---|
| **15-29 (n=165)** | **30.9** | **9.7** | **14.5** | **4.8** |
| **30-54 (n=1577)** | **27.2** | **10.0** | **8.1** | **7.4** |
| **55-84 (n=289)** | **37.0** | **12.1** | **9.0** | **13.5** |
| **p-value** | **<0.001** | **0.5** | **0.02** | **0.007** |

** Numbers may not up to the total because of the untyped 37 specimens.*

**Figure 2.** Distribution of hrHPV,lrHPV types and multple infections by age categories among HPV-positive women.




Exploration of the association of potential risk factors for HPV positivity for women at older ages, 55-84 years old, showed that no included variables, including marital relationship status combined with the number of cowives, lifetime sex partners, number of children, and contraception use, were significantly associated with the HPV-positivity for the study population (Table 6).

**Table 6.** Factors associated with women in the older age category, 55-84 ages (n=289)

| **Variables *** | **Women 55-84 ages (HPV pos/total)** | **HPV prevalence %** |
|---|---|---|

| | | |
|---|---|---|
| **HPV** | 107/289 | 37.0 |
| ***Relationship status*** | | |
| monogamous marriage | 26/55 | 47.3 |
| polygamous marriage 1 cowife | 21/66 | 31.8 |
| polygamous marriage >1 cowives | 23/76 | 30.3 |
| single, separated and widowed | 34/81 | 42.0 |
| | | p=0.14 |
| ***Lifetime sex partners*** | | |
| one | 52/158 | 32.9 |
| two and more | 50/121 | 41.3 |
| | | p=0.19 |
| **Number of Children** | | |
| 0-5 | 38/102 | 37.3 |
| 6 + | 69/186 | 37.1 |
| | | p=1.0 |
| **Education** | | |
| none | 83/217 | 38.2 |
| primary | 18/49 | 36.7 |
| secondary and university | 6/20 | 30.0 |

p=0.76

** Numbers may not up to the total because of the missing information.*

## IV. DISCUSSION

We found that age-specific HPV prevalence and proportion of hrHPV, lrHPV and multple infections differ across different age groups in Senegal. Overall HPV prevalence showed a bimodal age distribution with the first peak at age of 25-29 and the second peak at older ages, among women ≥65 years old. This result adds to the evidence of bimodal trends in the age-specific HPV prevalence in Africa (Awua et al., 2017; Xi et al., 2003) and world regions and countries (Smith et al., 2008). For example, in Senegal the study included women >35 reported greatest HPV prevalence among women aged 55 years and older (Xi et al., 2003), whereas in Nigeria, Kenya, and Mozambique, HPV positivity declined with age but reached a plateau at approximately 40 years of age (Awua et al., 2017; Smith et al., 2008). A bimodal prevalence of HPV was reported in the US among older women (Smith et al., 2008) and among Hispanic women with a second increase around 45 years (Shokar et al., 2020) , in China with peaks at the <20 and at >60 age group (Liu et al., 2014), and in Denmark at ages 35-40 years and 75 years (Hammer et al., 2015). As HPV is often acquired soon after sexual initiation (Winer et al., 2008) and is common among sexually active women, the actual first peak of HPV infection is most likely due to the high probability of exposure to infection and a lack of adaptive immune responses in younger women. However, the second peak in older women should be investigated. The high HPV prevalence among women around menopausal ages may be caused by the physiologic and immunologic dysregulation at menopausal transition (Althoff et al., 2009). Changes in sexual behaviors at older ages may also be one of the potential causes of higher HPV prevalence at older ages (Gravitt et al., 2013). Considering the higher prevalence

of hrHPV and multiple infections (high-risk and low-risk types together) in older women in our population compared to younger and mid-aged women and taking into account of hrHPV tendency of causing persistent infection (Crosbie et al., 2013; Luckett et al., 2021), we hypothesize that the second HPV prevalence peak at older ages might be the result of persistency or reactivation of latent HPV (Fu et al., 2016).

The overall HPV prevalence was 28.9% in female outpatients in this study. The prevalence was higher than the previously reported HPV prevalence in Senegal among women with normal cytology (10.5%, 13% and 27.1%) (Fall et al., 2019; Hanisch et al., 2013; Xi et al., 2003) . The difference might primarily be attributed to the fact that we included women of all ages, 15-84.

Numerous studies have determined the risk factors for HPV infection in females: new sex partnerships, increased numbers of lifetime sex partners, being married and non-monogamous relationships and contraception use (Chelimo et al., 2013; El-Zein et al., 2019). However, few have investigated the risk factors for HPV infections associated with age that would explain the increased prevalence of HPV infection among older women. It was found that early age at sexual debut and first pregnancy were risk factors among women 56+ years (Clarke et al., 2011). Although Clark et al. hypothesized that the number of cowives in a polygamous marriage correlates with hrHPV at older age, they did not find a significant association. Gravitt et al. established that lifetime sex partners of 5 and more is a risk for women aged 50-60 (Gravitt et al., 2013). Giuliano at al. presented significant association for sex partners >2 and HPV-positivity in age-adjusted model (Giuliano et al., 2005). Consistent with the other studies, we determined that age, relationship status, lifetime number of sex partners, and contraception use were significantly associated with the HPV infection. In contrast, we also looked for the association of the potential risk factors for women at older ages (>55 years). However, considering the small sample size (n=289 women >55 years old) and that none of the older

women used condoms and hormonal contraceptives, and none were smokers, we did not identify any significant risk factors associated with HPV positivity at older ages, 55-84 years.

Five most common hrHPV types, HPV58, 16, 52, 33 and 31, some of which occurred singlely and some in combination with other types, were detected among women of all ages. Women 55+ ages were most affected by multiple hrHPV and lrHPV (13.5%) types than younger and mid-aged women. Consistent with previous studies, identified hrHPVs are most common among women with normal cytology in Africa (de Martel et al., 2017; Ogembo et al., 2015) with the leading type being HPV16 (Keita et al., 2009; Ogembo et al., 2015; Okoye et al., 2021; Tagne Simo et al., 2021). There is a wide variation of HPV genotypes across African countries; HPV52 and HPV58 were the most frequent in Ghana (Debrah et al., 2021) and HPV58 and HPV16 were the most frequent in Benin (Tounkara et al., 2020) and Kenya (de Vuyst et al., 2010), while HPV31, 35 and 16 were the most common hrHPV type detected in Nigeria (Emeribe et al., 2021). These variations confirm the epidemiological particularity of circulating HPV types in West Africa.

***Strengths and implications***

We conducted a large study, with over 2,000 women, and is the first focused on older-aged women in Senegal. The large sample size allowed us to compare the HPV prevalence across different age groups and identify the bimodal HPV prevalence. In contrast to previous studies conducted in West Africa that set an age limit for the participants, women at 15-54 ages (Wall et al., 2005), >35 years old (Xi et al., 2003) and women aged 30-50 (Dykens et al., 2017), we included women of all ages (15-84 years old). Therefore, we were able to analyze the risk factors associated with HPV positivity and describe the prevalence of hrHPV, lrHPV, and multiple infections across a wide range of women. Further, advanced HPV-DNA testing was conducted to identify 38 HPV types among a substantially previously unscreened population.

We identified the highest HPV prevalence among older-aged women (>55 years) who would fall outside of the current screening recommendations. Recently implemented HPV vaccination in Senegal has focused on girls < 15 and began a few years ago, which may ultimately result in changes in patterns of HPV in Senegal. However, older unvaccinated women with high HPV prevalence are at continued risk for cervical cancer for decades. Therefore, considering the highest HPV prevalence among older women, the screening of older women may be even more important. WHO recommended HPV testing with 5 to10 year screening intervals perdominantly for women under 50 (World Health Organization 2021). Additional recommendation by the WHO for the women aged 50-65 years who have never been screened, is to provide screening when the tools are available. However, lack of resources and inadequate health infrastructure are still barriers for cervical screening uptake in Africa (Black et al., 2019; World Health Organization 2021) . Revising the screening intervals and age recommendations of women for the screening programs in LMIC may help prevent women at older ages with persistent hrHPV infections from developing cervical cancer.

Understanding the distribution of HPV genotypes among different age groups is crucial to estimating the burden of HPV infections. The current vaccine used in Senegal protects against HPV 16 and HPV 18, and 2 lrHPV types (6 and 11). However, HPV types 58 and 52 predominant in our population, and cause cervical cancer apart from HPV 16 and HPV 18. Moreover, the current vaccination program in Senegal could prevent 25.4% of hrHPV infections in our population, while 91.2% of hrHPV infections are vaccine-preventable with the nonvalent formulation. The initiation of a nonavalent vaccine for routine vaccination of females may be one of the most promising strategies to decrease the HPV burden.

***Limitations***

There are several possible limitations in our study. We analyzed the data extracted from two studies conducted from 2002 to 2010 in Senegal. Though we know that the historical data gathered prospectively by direct subject interviews are complete, still, because of its retrospective nature, this study might be subject to residual confounding in the analysis of risk factors. To deal with this, we adjusted for a large number of potential confounding variables based on the literature, however, no data were available on the age of the first sex and age of the first pregnancy. Despite the large overall sample size, which allowed us to identify a substantial second peak of HPV in older women, the relatively small sample size among older women precluded us from identifying significant risk factors associated with HPV in older women. Finally, our study results have limited generalizability to non-urban sites because participants were recruited from two clinics in Dakar, the capital city, and the majority of data were collected from home addresses in Dakar.

## V. CONCLUSION

We presented a cross-sectional study of baseline data on HPV prevalence in Senegal, West Africa from 2002-2010. HPV prevalence showed bimodal age distribution with a peak at the 25-29 ages and the second one in older women aged 65 and above. HPV 58, 16, 52, 33 and 31 were the most commonly identified hrHPV types among the study population.

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