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Human papillomavirus prevalence and type-specific distribution of high- and low-risk genotypes among Malagasy women living in urban and rural areas

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ABSTRACT

Background: Cervical cancer (CC) is the most common cancer among sub-Saharan African women. Efficient, global reduction of CC will only be achieved by incorporation of human papillomavirus (HPV) vaccination into existing programmes. We aimed to investigate the overall and type-specific prevalences and distributions of oncogenic HPVs.

Methods: A total of 1081 women aged 30–65 years were recruited to three sequential studies in Madagascar. Demographic and historical data were obtained from participants, and specimens were self-collected for HPV testing using real-time polymerase chain reaction. HPV-positive women underwent detailed pelvic examination, visual inspection of the cervix with acetic acid, biopsy, and endocervical curettage. Data were analysed using χ^2 and *t*-tests, and logistic regression.

Results: The prevalence of all 19 high-risk types of HPV was 39.3%. There were no differences in the prevalences of HPV and CC between rural and urban Malagasy women. The most common high-risk HPV types were HPV-53 (6.2%) and HPV-68 (5.8%), followed by HPV-52 (5.2%), HPV-35 (4.5%), HPV-73 (3.4%), HPV-31 (3.4%), HPV-16 (3.1%), and HPV-18 (3.1%). The prevalence of cervical intraepithelial neoplasia $\geq$ grade 2 (CIN2+) was 9.4%. CIN1–CIN3 lesions were more common in women in their 30s. The median age of participants with CIN2+ was 44 years (range 37–55). Overall, 25.8% of CIN2+ cases were associated with HPV-16/18.

Conclusions: This study provides evidence to support the introduction of HPV vaccination in eastern African countries such as Madagascar. Further studies are needed to screen younger women and adolescents, to provide a global vision of HPV genotype distributions and to maximize the impact of HPV vaccination.

1. Introduction

Cervical cancer (CC) is the most common cancer among sub-Saharan African women [1]. Over 80% of all new cases are diagnosed in the developing world, where it is the second most common cancer affecting women [2]. Madagascar has about 3194 new CC cases per year, and 1804CC-related deaths occurred in 2012, giving it the 11th highest incidence of CC worldwide [2].

Madagascar is an island off the coast of Southeast Africa and has an estimated female population aged $\geq$15 years of 6.68 million [3], with an estimated life expectancy of 59 years [4]. These women are at risk of developing CC. Furthermore, approximately 0.3% of the population aged 15–49 is infected with HIV [3].

Organized screening programmes, as well as early treatment of cervical pre-cancer, has led to reductions in the incidence of CC and related mortality in Western countries [5,6]. However, these programmes are costly and complex to implement in developing countries. Madagascar has no national CC screening recommendations, though visual inspection methods for CC screening are available through pilot projects organized by the Ministry of Health or non-governmental organizations (NGOs). In the

Abbreviations: CC, cervical cancer; HR-HPV, high-risk HPV; HPV, human papillomavirus; LR-HPV, low-risk HPV; Self-HPV, self-sampling for HPV testing.

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absence of changes in prevention and control measures, CC deaths in Madagascar are expected to increase to >2000 per annum by 2025 [7].

Most cases of CC and pre-cancer are caused by persistent infection with oncogenic human papillomavirus (HPV) [8]. Prophylactic HPV vaccines have thus been developed to protect against HPV infection, and offering HPV vaccination to all girls before exposure to HPV infection represents the start of a global effort to prevent CC. Forty-five countries had introduced HPV vaccination by the end of 2012, according to the World Health Organization (WHO) [7], though vaccination was largely restricted to developed countries because of the high associated costs. HPV vaccination in low-resource countries currently relies on partial subsidy of the vaccine by NGOs and other companies [9], and its widespread implementation in the near future appears to be limited [10]. The efficient, global reduction of CC will thus only be achieved when developing countries reallocate their public health resources to incorporate HPV vaccination into existing programmes. In Madagascar specifically, HPV vaccination is still not available to all the population; a demonstration vaccination programme was provided by Gavi The Vaccine Alliance and implemented by the Ministry of Health in two pilot districts in 2013.

Reliable country- and population-specific epidemiological data for HPV and CC need to be determined to maximize the impact of vaccination. However, there are currently no official WHO estimates of the prevalence or type-specific distribution of HPV in representative population-based samples of women in Madagascar. We therefore assessed the type-specific distributions of high- and low-risk HPV genotypes among women aged 30–65 years living in rural and urban areas in Madagascar. We aimed to investigate both the overall and type-specific prevalences and distributions of oncogenic HPVs, as well as estimating the associations of various factors with HPV infection in each setting. This information will help in assessing the importance of HPV vaccination in this population.

2. Materials and methods

2.1. Study design and enrolment

The study was conducted by the University Hospitals of Geneva in collaboration with the Saint-Damien Healthcare Centre in Ambanja, Madagascar, and the Health and Family Planning Ministry. It included data from three sequential CC screening campaigns carried out among Malagasy women between 2013 and 2015 [11,12]. Overall, 300 women were recruited to the first campaign, 332 to the second, and 449 to the third campaign ($n = 1081$). Criteria for inclusion in the study were age 30–65 years and written informed consent signed before participation. Exclusion criteria for all three studies were pregnancy beyond 20 weeks and former conisation or hysterectomy. The screening campaign was advertised through women's associations, churches and local radio stations.

Ethical approval was obtained from the Malagasy National Commission for the Ethics of Science and Technology and from the Ethical Cantonal Board of Geneva, Switzerland (CER: 14-071).

2.2. Data and specimen collection

Women aged 30–65 years were enrolled for HPV-testing by self-collecting a vaginal sample (self-HPV) using a sterile, cotton-tipped swab in a dry tube. Recommendations were to hold the swab by the end of the handle, insert the swab into the vagina until resistance, avoid contact with the external genitalia, gently turn the swab three times, and remove it. The dry swab was then stored and transported at ambient temperature. Self-HPV was always performed without supervision. Participants were also asked to complete a questionnaire regarding socio-demographic information. With regard to professions, 'independent' women were defined as self-employed. A 'housewife' was defined as a woman whose main occupation was caring for her family and doing housework.

2.3. HPV analysis

HPV analysis was performed by semi-quantitative real-time multiplex polymerase chain reaction (PCR) assay for screening and HPV genotyping (Anyplex II HPV28 (H28) test; Seegene, Seoul, South Korea). DNA extracts were subjected to amplification and detection using the H28 test and CFX96 real-time thermocycler (Buhlmann Laboratories AG, Schönenbuch, Switzerland). Data recording and interpretation were automated. Details of the procedure and evaluation have been described previously [13,14]. H28 used dual-priming oligonucleotides and tagging oligonucleotide cleavage and extension technologies for simultaneous detection of 19 high-risk HPVs (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82) and nine low-risk HPVs (types 6, 11, 40, 42, 43, 44, 54, 61, and 70).

2.4. Follow-up

All women who tested positive for high-risk HPV genotypes underwent detailed pelvic examination, visual inspection of the cervix with acetic acid (VIA), and colposcopy. VIA was performed as recommended by the WHO [15]. When a cervical lesion was identified, lesion-directed biopsy and endocervical curettage were performed; if the lesion was considered non-pathological, cervical biopsy at the 6 O'clock position and endocervical curettage were performed, using biopsy forceps and an endocervical brush, respectively. Cervical cytology was also performed in all patients using the ThinPrep Pap test (Hologic, Bedford, MA, USA).

In general, all lesions were considered pathological if the colposcopy results were abnormal, even if no lesion was detected by VIA assessment. All eligible women with abnormal results after the gynaecological examination were treated. Women with biopsy-proven CIN2+ lesions were also treated. HPV tests and histological specimens were analysed in a laboratory in Switzerland.

2.5. Data analysis and statistics

Data were analysed using StataCorp 2013: Stata Statistical Software 13 (College Station, TX, USA). HPV prevalence was calculated as the proportion of women who tested positive for high-risk HPV types. Women co-infected with high- and low-risk genotypes were categorized as high-risk-HPV-positive.

Women in rural and urban areas of Madagascar were compared in terms of their sociodemographic characteristics, reproductive history, number of sexual partners, HPV and disease status, by descriptive analyses. The frequency distributions of both high- and low-risk HPV genotypes were represented. Categorical variables were analysed by Pearson's χ^2 or Fisher's tests, and continuous and ordinal variables were analysed by Student's t-tests. HPV-positive and -negative women were similarly compared.

Univariate and multivariate logistic regression methods were used to identify factors strongly associated with HPV prevalence. A value of $p < 0.05$ was considered statistically significant. Odds ratios (OR) were adjusted for potential confounders such as age, marital status, number of lifetime sexual partners, and parity, and 95% confidence intervals (95% CI) were calculated.