original reports abstract

Prevalence and Subtype Distribution of High-Risk Human Papillomavirus Among Women Presenting for Cervical Cancer Screening at Karanda Mission Hospital

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PURPOSE High-risk human papillomaviruses (hrHPV) are the primary cause of cervical cancer. Human papillomavirus (HPV) vaccination is expected to prevent cervical cancers caused by the HPV types included in vaccines and possibly by cross-protection from other types. This study sought to determine the hrHPV type distribution in women at a rural Zimbabwe hospital.

METHODS We implemented a cross-sectional study at the Karanda Mission Hospital. Using the Visual Inspection with Acetic Acid Cervicography technique, clinicians collected cervical swabs from 400 women presenting for screening for cervical cancer. Samples were initially analyzed by Cepheid GeneXpert; candidate hrHPV genotypes were further characterized using the Anyplex II HPV28 Detection Kit.

RESULTS Twenty-one percent of the 400 women were positive for a high-risk genotype when using the GeneXpert analyzer; 17% were positive when using the multiplex analysis. Almost two thirds of the hrHPV women had a single DNA type identified, whereas one third had multiple genotypes, ranging from 2 to 5. hrHPV was observed more frequently in HIV-positive than in HIV-negative women (27% *v* 15%). Of the 113 isolates obtained, 77% were hrHPV genotypes not included in the bivalent or quadrivalent vaccines, and 47% represented DNA types not covered in the nonavalent vaccine. Forty-seven percent of the women with hrHPV harbored a single genotype that was not covered by the nonavalent vaccine.

CONCLUSION A large fraction of hrHPV isolates from women participating in a cervical cancer screening program in northern Zimbabwe are DNA types not covered by the bivalent, quadrivalent, or nonavalent vaccines. These findings suggest the importance of characterizing the hrHPV DNA types isolated from cervical neoplasia in this population and determining whether cross-immunization against these genotypes develops after administration of the vaccines in current use.

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INTRODUCTION

Globally, cervical cancer is the fourth most common cancer and the fourth-leading cause of cancer death in women.[1] Women in low- and middle-income countries are disproportionately affected, accounting for 85% of all cervical cancer–related deaths.[2] In these countries, poor survival rates are associated with poor infrastructure, lack of trained health care providers and available treatment options, and high costs of treatment.[3-5]

Zimbabwe ranks fourth in age-standardized cervical cancer incidence rates.[6] Cervical cancer is the most common cancer among women in Zimbabwe.[7] The estimated incidence is 52.1 per 100,000 women, and the age-adjusted mortality rate is 43.1%[7]; actual rates are likely much higher than these, given underreporting in rural areas.[8,9]

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections worldwide. High-risk or oncogenic strains are associated with the development of premalignant and malignant epithelial lesions of the female and male anogenital tract.[10,11] More than 95% of cervical cancers are caused by infection of the cervical epithelium with high-risk human papillomavirus (hrHPV).[12] HPV is also considered a comorbid opportunistic infection in the setting of HIV infection.[13] Despite successful antiretroviral therapy, some authors have described rising HPV infections among HIV-positive individuals.[14]

Of central importance to Zimbabwe's cancer strategy is the prevention and early detection of this disease. Supported financially by Gavi, the Vaccine Alliance, the Ministry of Health and Child Care Zimbabwe sponsored pilot projects that delivered HPV vaccinations to girls 10-14 years of age, using the bivalent HPV

ASSOCIATED CONTENT
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What fraction of high-risk human papillomavirus (hrHPV) isolates from women participating in a cervical cancer screening program in Zimbabwe represent DNA types not covered by the bivalent, quadrivalent, or nonavalent vaccines currently in use?

Knowledge Generated

Seventy-seven percent of the hrHPV genotypes were not covered by the bivalent or quadrivalent vaccines, and 47% of the hrHPV genotypes were not covered by the nonavalent vaccines. Forty-seven percent of women with hrHPV harbored a single genotype that was not covered by the nonavalent vaccine.

Relevance

The possibility that oncogenic genotypes are not being neutralized by the vaccines in use presents a significant theoretical challenge to the effectiveness of a vaccination program; more research is required to determine the extent to which these vaccines generate cross-protection against these specific hrHPV subtypes.

vaccine.[15] The quadrivalent HPV vaccine has been used in other settings.[16] The bivalent vaccine confers protection against HPV 16 and 18, and the quadrivalent against HPV 6, 11, 16, and 18 (the first 2 are understood to be non-oncogenic). HPV types 16 and 18 are reported to be responsible for approximately 70% of cervical cancers in women.[12,17] These vaccines have been shown to be highly effective in preventing high-grade cervical lesions.[18] A nonavalent vaccine is also available and covers an additional 5 oncogenic subtypes of HPV, including HPV 31, 33, 45, 52, and 58, and has been associated with additional reductions in the incidence of cervical intraepithelial neoplasia.[19]

The prevalence of hrHPV genotypes seems to vary geographically. A study consisting of HIV-negative women in Zimbabwe showed that HPV 58 was more common than HPV 16 or 18,[20] whereas a study of women with invasive cervical cancer in Harare showed that HPV 16 was the most prevalent high-risk genotype, followed by HPV 33.[21] In a study conducted in rural Zimbabwe, HPV 35 was found to be the most common genotype, followed by HPV 33 and HPV 58.[22] The possibility of oncogene genotypes incompletely or not at all neutralized by the bivalent, quadrivalent, or nonavalent HPV vaccines presents a significant theoretical challenge to the effectiveness of a vaccination program.[9]

In a coordinated effort with the nation's cancer control strategy, the Karanda Mission Hospital (KMH) initiated a screening program using Visual Inspection with Acetic acid and Cinematography (VIAC). The current study was launched to establish the prevalence of hrHPV in women presenting for screening, to characterize the distribution of genotypes in rural northern Zimbabwe, and to identify and quantify hrHPV DNA types not represented in the vaccines being deployed throughout the nation.

METHODS

Study Design

We conducted a prospective cross-sectional study of women presenting for cervical cancer screening (VIAC) to KMH, a community hospital located in the Mt Darwin district of rural Zimbabwe. The study was approved by the Joint Research Ethics Committee for the University of Zimbabwe and the Medical Research Council for Zimbabwe (Prevalence and Subtype Distribution of Cervical High-Risk Human Papillomavirus Among Women Presenting for Cervical Cancer Screening at Karanda Mission Hospital, protocol proposal submitted to Medical Research Council Zimbabwe). Participants were recruited to a total of 400 participants.

This sample size was chosen on the basis of the assumptions that, in the Mt Darwin region, the HPV prevalence in HIV-negative and HIV-positive individuals is 5% and 20%, respectively. The HIV prevalence was estimated at 20% (the current HIV prevalence rate among VIAC patients at KMH).

Participants

The study consisted of sexually active female patients 30 to 65 years of age, living in the Mt Darwin district, and presenting to KMH for screening as part of the VIAC program. Eligible participants were invited to participate in the study after they were given a thorough description of the study's goals, and informed consent was obtained from all participants. Patients were excluded if they had a history of cervical cancer or precancerous lesions, had a history of a hysterectomy, or had never engaged in sexual intercourse. If HIV status was not documented or was unknown, an HIV counselor offered rapid HIV testing and counseling. Nurses used a questionnaire to gather data regarding the participants' age, parity, contraception use, and HIV status.

Specimen Collection and hrHPV Typing

Nurses were trained in obtaining a sample for HPV analysis. Cervical brushes were used to collect specimens that were then dropped into a collection vial with 3 mL ThinPrep PreservCyt liquid media. Specimens were tested in an onsite laboratory using the GeneXpert HPV assay. Positive

specimens were transported to the African Institute of Biomedical Science and Technologies Laboratory in Harare, where DNA extraction and subtyping were performed using multiplex analysis. Briefly, DNA was extracted using the QIAamp MiniElute Virus Spin kit per the manufacturer's instructions. HPV genotyping was performed using the Anyplex II HPV28 Detection kit (Seegene, Seoul, Republic of Korea) on a BioRad CFX-96 real-time thermocycler per the manufacturer's instructions. Twenty-eight HPV genotypes (19 high risk and 9 low risk) were tested in each sample. The 19 high-risk genotypes tested were HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82. The 9 low-risk genotypes tested were HPV 6, 11, 40, 42, 43, 44, 54, 61, and 70. Results of both VIAC and HPV testing were communicated to participants.

Statistical analysis was performed using SAS 9.4. Type-specific hrHPV prevalence was calculated with an exact binomial distribution–based 95% CI. Overall hrHPV prevalence was determined in the HIV-positive and HIV-negative groups.

RESULTS

Participants

A total of 400 women were recruited into the study and elected to undergo screening for cervical cancer with VIAC at the KMH. Table 1 summarizes the baseline characteristics of the participants.

Distribution of High-Risk HPV Genotypes

Among the entire cohort of women, 21% (83 of 400) were positive for a high-risk genotype when using the GeneXpert analyzer. Subsequently, 17% (67 of 400) were positive when subjected to multiplex analysis. The data that follow are derived from the 67 samples analyzed by the multiplex technique.

Sixty-four percent of the hrHPV-positive women had a single virus type isolated, whereas approximately one third were infected by multiple DNA types ranging from 2 to 5 per sample (Fig 1). A total of 113 hrHPV isolates were analyzed from the cohort.

Among the cohort of sampled women, 18.5% (74 of 400) were HIV positive. Of the 67 hrHPV-positive individuals, 18 (27%) were HIV positive. The distribution of DNA types in the total population of hrHPV-positive women and the distribution in the hrHPV HIV-positive women are demonstrated in Figure 2.

Coverage of Isolates by HPV Vaccines

Among the 113 isolates obtained from 67 women, 87 (77%) represented hrHPV DNA types that were not covered in the quadrivalent vaccine (types 6, 11, 16, and 18), as listed in Table 2. Of the 113 isolates, 53 (47%) represented DNA types not covered in the nonavalent vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58), as listed in Table 3.

Among the genotypes not included in the 9-valent vaccine, this study identified DNA types 35, 39, 51, 53, 56, 66, 68, 69, 73. Fourteen (47%) of the 30 women harboring hrHPV not covered by the 9-valent vaccine demonstrated a single DNA type as the only virus identified.

TABLE 1. Demographics and Clinical Characteristics of Study Participants

Variable	No. (%)	Mean (standard deviation)
Age, years		42.20 (9.54)
Parity		4.28 (2.07)
0	6 (1.50)	
1	14 (3.50)	
2	60 (15.00)	
3	73 (18.25)	
4	77 (19.25)	
5	61 (15.25)	
≥ 6	104 (26.00)	
Missing	5 (1.25)	
Contraception		
Jadelle	16 (4.00)	
Combined oral contraceptive pill	248 (62.00)	
No contraceptive use	29 (7.25)	
Depo Provera	58 (14.5)	
Condoms	5 (1.25)	
Bilateral tubal ligation	1 (0.25)	
Progestin-only pill	40 (10.00)	
Missing	3 (0.75)	
HIV status		
Positive	74 (18.5)	
Negative	326 (81.5)	

DISCUSSION

The results of our study demonstrate a high hrHPV prevalence in rural Zimbabwe, as well as a high proportion of hrHPV genotypes not covered by the quadrivalent or nonavalent vaccines. In our study, hrHPV prevalence by

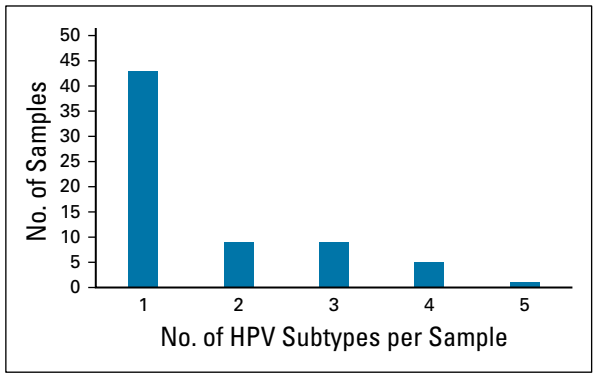

FIG 1. No. of human papillomavirus (HPV) subtypes in high-risk human papillomavirus–positive samples.

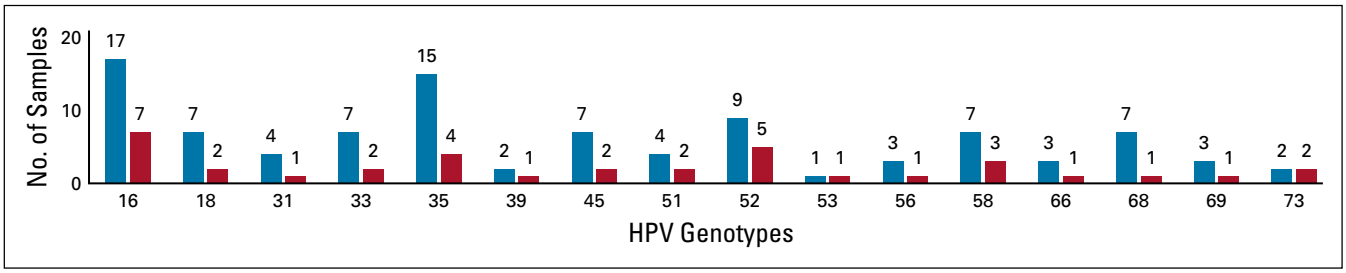

FIG 2. Distribution (ordinate) of DNA types (abscissa) in the total population of high-risk human papillomavirus (hrHPV)–positive women and the distribution in the hrHPV HIV-positive population: hrHPV in HIV-negative and HIV-positive women (blue); hrHPV in HIV-positive women (red). HPV, human papillomavirus.

the GeneXpert HPV assay was 21%. A recent community-based cross-sectional study in rural Zimbabwe using GeneXpert HPV found a similar HPV prevalence of 17%.[23] These rates are higher than those previously seen in the United States and Europe.[24]

We found that hrHPV infection was more common among HIV-positive women than among HIV-negative women (28% of HIV-positive women *v* 15% of HIV-negative women), which is consistent with the findings of prior studies.[14,25,26] HIV-positive women in sub-Saharan Africa have a higher prevalence of hrHPV infection and a greater proportion of infections with multiple hrHPV genotypes.[27,28] These findings emphasize the importance of screening for cervical cancer in all women, with particular urgency for those who are HIV positive.

Our data also highlighted the representation of hrHPV genotypes other than HPV 16 and 18 in the Mt Darwin district in rural Zimbabwe. These include HPV 35, 45, 52, 58, and 68. Fitzpatrick et al[23] also found high levels of these types in the Hurungwe district of Zimbabwe. Supporting this point is a prior study that demonstrated high levels of types other than HPV 16 and 18 in rural Zimbabwe.[22] Of the 113 hrHPV types identified among women in our study, 15 were HPV 35 and 7 were HPV 68. Both HPV 35 and HPV 68 are not included in any hrHPV vaccine. In the aggregate, 77% of the identified hrHPV DNA types are not covered by the quadrivalent vaccine, and 47% are not covered by the nonavalent vaccine. Considering the frequency with which women are infected with non–vaccine-covered genotypes, it is important to determine whether the identified DNA types are oncogenic in the population under study.

The patients in this study were women who presented for cervical cancer screening. Among these, 15 of the 67 hrHPV-positive women were VIAC positive or harbored lesions specific for cancer. Of interest, 5 women (33%) harbored a genotype not covered by the available vaccines. This suggests the importance of additional research to determine the HPV genotypes in preneoplastic and frank invasive cancer in this population. This information, if consistent with the findings in this study, will encourage the development of vaccines likely to provide optimal protection.

It is important to consider the possibility of cross-immunization, the process by which antibodies to the hrHPV virus-like particles used in the vaccine are able to neutralize virions of related HPV types and thereby prevent disease.[28,29] Harper et al[30] demonstrated partial cross-protection of the bivalent HPV vaccine against HPV 31 and 45. Bivalent vaccination programs have been shown to decrease the population prevalence of HPV genotypes not covered by the vaccine; however, the same study identified low levels of cross-protection with high-risk DNA types other than HPV 31, 33, and 45.[31] Prior studies from Brown et al[32] and Wheeler et al[29] showed low-to-moderate cross-protection against hrHPV types related to HPV 16 and 18. Herrero[33] analyzed the major findings in these 2 studies and noted that the only significant cross-protection against cervical intraepithelial neoplasia 2-3 or adenocarcinoma in situ lesions was protection against HPV 31, which is most related to HPV 16. Furthermore, Wheeler et al[29] performed an intention-to-treat analysis of women who received at least 1 dose of vaccine and returned for follow-up care, regardless of infection status at the start of the study. Among this "catch-up vaccination" population, there was no significant protection against advanced lesions with any combination of HPV types.[33] Data from 2 randomized controlled trials showed no statistically

TABLE 2. Percentage of hrHPV Covered or Not Covered by Bivalent or Quadrivalent Vaccine

Coverage	No. of hrHPV Genotypes	% (95% CI lower to upper limit)
Not covered	87	77 (68 to 84)
Covered	26	23 (15 to 32)

Abbreviation: hrHPV, high-risk human papillomavirus.

TABLE 3. Percentage of hrHPV Covered or Not Covered by Nonavalent Vaccine

Coverage	No, of hrHPV Genotypes	% (95% CI lower to upper limit)
Not covered	53	47 (37 to 56)
Covered	60	53 (43 to 62)

Abbreviation: hrHPV, high-risk human papillomavirus.

significant cross-protection against persistent infection with HPV 52 or HPV 58.[34,35]

The Karanda and Chidamoyo studies indicated that a substantial number of DNA types are not known to be neutralized by any of the vaccines in current use. Cross-protection against the uncovered genotypes identified in rural Zimbabwean women in this study cohort has not been investigated. Additional research is needed to elucidate the frequency with which uncovered high-risk genotypes contribute to the development of cervical intraepithelial neoplasia or cancer, as well as the extent to which vaccines generate cross-protection against these hrHPV subtypes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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