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Human Papillomavirus Genotype Distribution Patterns in Zimbabwe: Is the Bivalent Vaccine Sufficient?

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Abstract

Background: Vaccination against human papillomavirus (HPV) is the primary preventative strategy that has been shown to reduce the burden of HPV-related diseases. Zimbabwe introduced the bivalent vaccine (HPV 16/18) in the vaccination program targeting prepubescent girls in 2018. This review is an analysis of the distribution of HPV genotypes from various studies conducted in Zimbabwe to ascertain the effectiveness of the bivalent vaccine and make recommendations for future HPV vaccine choices. ***Summary:*** Zimbabwean studies have mostly reported on cervical HPV in the urban areas. The most frequent HPV genotypes from cervical sites were 16, 18, 33, 35, 45, 56, and 58. These were identified from samples with normal cytology, pre-cancer, and invasive cervical cancer. The few studies that have been done in rural areas reported HPV 35 as the most frequent cervicovaginal genotype. From the anal region of individuals reporting for routine screening, HPV 16, 18, 35 52, and 58 were the most frequent. A study on genital warts identified HPV 6, 11, 16, 40, 51, and 54. In a study on children with recurrent respiratory papillomatosis (RRP), HPV 6 and 11 were the most common and HPV 35 was also identified in these children. There are no available published data on HPV distribution in head and neck cancers in Zimbabwe. ***Key Messages:*** Given that 83% of cervical cancers in Zimbabwe are caused by HPV 16/18, the bivalent vaccine could cover a significant proportion of HPV-related cervical cancer. The current limitation of the bivalent vaccine is its failure to prevent benign lesions such as genital warts and RRP or all cervical cancer cases in Zimbabwe. For the prevention of most HPV-related conditions, the nonavalent vaccine would be the most appropriate option for the Zimbabwean population. Currently, there is no vaccine that includes HPV 35, yet this genotype was frequently identified in HPV-related diseases. Vaccine developers may need to consider HPV 35 when manufacturing the next-generation HPV vaccines. Furthermore, boys should also be included in HPV vaccination programs to improve herd immunity, as well as prevent RRP- and HPV-related head and neck cancers.

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Introduction

Human papillomaviruses (HPVs) are double-stranded DNA viruses that infect predominately mucosal epithelial cells. Based on oncogenic ability, HPV genotypes are assigned to low-risk HPV (lrHPV) and high-risk HPV (hrHPV) [1]. hrHPV genotypes have been identified as aetiological agents of anogenital cancers such as in 99% of cervical, 80–85% of anal, 50.8% of penile, and 67–78% vulvovaginal l cancers, as well as non-anogenital cancers such as in 30–40% of head and neck squamous cell carcinomas; ranging between 30 and 40%, with much lower estimated rates for the other areas, like 2.1–4.4% for oral cavity and 2.7–3.5% for larynx and hypopharynx cancers [2–6]. Low-risk genotypes of HPV are associated with anogenital warts and recurrent respiratory papillomatosis (RRP) [7]. The HPV vaccinations are the primary preventative strategy that has been shown to reduce the burden of HPV-related diseases [1]. Prior to vaccination, secondary screening/early detection methods such as Pap smears and visual inspection with acetic acid were the only prevention available [8].To date, there are three FDA-approved prophylactic HPV vaccines; Cervarix™ (Bivalent), Gardasil (Quadrivalent), and Gardasil-9 (nonavalent) [9, 10]. The bivalent vaccine includes HPV 16 and 18 genotypes; the quadrivalent vaccine adds low-risk types HPV 6 and 11 as well as HPV 16 and 18 while the nonavalent vaccine (Gardasil-9) protects against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 [9, 11]. In 2018, the Government of Zimbabwe through the Ministry of Health and Child Care (MoHCC) implemented a nationwide HPV vaccination program of prepubescent girls, using the bivalent vaccine [1]. The vaccine is made through recombinant DNA technology. Recombinant DNA technology allows expression of the L1 major capsid protein of HPV in different expression systems, e.g., baculovirus, which has an intrinsic capacity to self-assemble into viral-like particles. Viral-like particles are non-infectious, highly immunogenic, and can elicit neutralising antibodies [12]. The bivalent vaccine showed 93.2% vaccine efficacy against CIN3+ in global clinical trials [13], with some studies following vaccinated individuals for more than 10 years and finding no evidence of protection decreasing over time [14]. This review aimed to review the studies that have been done in Zimbabwe to ascertain the distribution of HPV genotypes in studies conducted in Zimbabwe and ascertain the sufficiency of this bivalent vaccine in protection against HPV-related diseases and make recommendations for future HPV vaccine choices.

Coverage of HPV Vaccination in Zimbabwe

The government of Zimbabwe through the MoHCC introduced bivalent HPV vaccine with a two-dose 1-year schedule to all 10- to 14-year-old girls using a pulsed-campaign approach in May 2018 (dose 1) and May 2019 (dose 2) where about 98% of the vaccines were delivered at schools [15]. As of October 24, 2022, Zimbabwe had achieved an HPV vaccine coverage of 40% and 67% for the second and first doses, respectively, in the target population [16].

HPV Distribution in Zimbabwe

There is geographic variation in the distribution of HPV genotypes. Globally, HPV 16 and 18 are the most common genotypes, accounting for 70% of cervical cancer cases [17]. HPV genotypes 31, 33, 35, 45, 52, and 58 account for an additional 20% of cervical cancers worldwide [17]. In a review of HPV distribution in African countries, Nigeria, Ghana, South Africa, and other sub-Saharan African countries, HPV 16, 58, 35, 45, 33, and 52 were reported as the most common genotypes, in order of their decreasing frequencies [18–23]. There are a relatively small number of articles reporting HPV genotype distribution in Zimbabwe. From PubMed and Google Scholar search, only 21 publications could be retrieved. The search included all publications that analysed the genotypes from all sites in Zimbabwe published by April 29, 2023. The search terms "HPV," "Genotypes," "Distribution," and "Zimbabwe" were used to identify publications describing the distribution of HPV genotypes in the Zimbabwean population. Publications that reported HPV genotypes outside Zimbabwe were excluded from the manuscript. Although Womack et al. [24] and Hove et al. [25] published the first papers on HPV DNA detection from Zimbabwe in 2000, they did not specify the HPV genotypes detected. All the retrieved studies, describing HPV genotypes in Zimbabwean sample sets, are listed in Table 1. The sensitivity and specificity of the methods used are summarised in Table 2. In this review, the distribution of HPV genotypes from Zimbabwe is briefly described, in both non-cancer and histology-confirmed cancer cases.

Distribution of HPV Genotypes in Non-Confirmed Cancers in Zimbabwe

Most studies that have been done in Zimbabwe to investigate HPV genotypes focused on anogenital sites, particularly the cervix. Up to the time of this review

Table 1. Summary of HPV studies carried out in Zimbabwe

Authors and year published [reference]	Sample size (anatomical region/diagnosis)	Top 4 HPV genotypes detected in descending order of frequency	Laboratory diagnostic methods
Womack et al. 2000 [24]	2,140 (cervical)	Not specified	Hybrid capture 2
Hove et al. 2000 [25]	23 (cervical)	Not specified	In situ hybridisation and Immunohistochemistry
Chirara et al. 2001 [26]	119 (histologically confirmed cervical)	Not specified	PCR
Stanczuk et al. 2003 [27]	43 (cervical)	16, 33, 18, and 31	Nested PCR and RFLP
Stanczuk et al. 2003 [28]	98 (cervical)	16, 33, 18, and 31	Nested PCR and RFLP
Baay et al. 2004 [29]	236 (cervical)	35, 58, 33, and 18	PCR
Fukuchi et al. 2009 [30]	2040 (cervical)	58, 16, 70, and 18	PCR and hybridisation
Averbach et al. 2010 [31]	631 (cervical)	16, 35, 51, and 52	PCR and hybridisation
Smith-McCune et al. 2010 [32]	2,040 (cervical)	58, 16, 70, and 18	PCR and hybridisation
Nowak et al. 2011 [33]	631 (cervical)	Not specified	PCR
Lowe et al. 2012 [34]	4 (skin)	1, 2, 5, 6, 16, and 52*	PCR and sequencing
Sebata and Chin'ombe 2017 [35]	125 (cervicovaginal)	81, 53, 6, and 90	PCR and sequencing
Matuvhunye et al. 2016 [36]	30 (cervical)	6, 16, 58, and 52	Inhouse nested PCR and Sanger sequencing
Dube Mandishora et al. 2017 [37]	144 (cervicovaginal and anal)	18, 52, 16, and 58	Illumina sequencing
Mudini et al. 2018 [38]	107 (histologically confirmed cervical)	16, 18, 56, and 33	Dot blot hybridisation
Chinyowa et al. 2018 [39]	122 (anal)	11, 58, 31, and 53	Dot blot hybridisation
Matinhira et al. 2019 [7]	52 (respiratory papillomatosis)	6, 11, 16, and 18	Illumina sequencing
Fitzpatrick et al. 2019 [40]	643 (cervicovaginal)	35, 18, 52, and 68	Anyplex PCR
Manyere et al. 2019 [41]	100 (genital warts)	11, 6, 16, and 40	Dot blot hybridisation
Marembo et al. 2019 [42]	136 (cervicovaginal)	52, 18, 16, and 58	Inhouse multiplex PCR

*All the genotypes were detected in all 4 teenagers.

Table 2. Sensitivity and specificity of commonly used HPV testing methods

Laboratory diagnostic methods for HPV detection	Sensitivity, %	Specificity, %
Hybrid capture 2	91.1	83.7 [43]
In situ hybridisation and immunohistochemistry	97.4	33.4 [44]
GP5+/6+-PCR	98.2	92.4 [45]
MY9/11 PCR	87.9	38.7 [46]
PCR and dot blot hybridisation	90.4	99.1 [47]
Next-generation sequencing	97.7	98.0 [48]
Anyplex PCR	98.3	93.6 [49]

article, none of the available studies gave data for the whole nation (population-based HPV genotype surveillance). Most researchers focused on Harare, the capital city of the country. The Methods for Improving Reproductive Health in Africa (MIRA) trial is the largest study to describe HPV genotypes in Zimbabwe, in a randomised control trial to assess latex diaphragm/lubricant gel provision in HIV and HPV acquisition from 2040 women from Harare. The MIRA trial reported HPV 58 (5.0%), 16 (4.7%), 70 (2.4%), and 18 (2.3%) in their decreasing frequencies, as the most common genotypes [50]. Another study recruited 145 HIV-infected and 446 HIV-uninfected women aged 18–35 in Chitungwiza and Harare from November 1999 to 2004 and reported HPV 16 (8.8%), 35 (6.3%), 51 (5.1%), 52 (5.4%) 58 (7.6%), and 68 (5.3%) as the most common genotypes in their decreasing frequencies [31]. The study utilised PGMY 09/11 L1 consensus primer system for HPV detection (HPV Linear Array, Roche Diagnostics, Indianapolis, IN, USA), and type-specific infection was determined using hybridisation with probes. This study reported that the odds of acquiring HIV were 2.4 times higher in women with prior cervical HPV infection after adjustment for behavioural and biologic risk factors, although the HPV genotypes were not stratified according to HIV status [31]. In that study, HPV-infected women were followed over time and 29–50% of new HPV infections developed into persistent infections. HPV 16, 18, 31, 33, 52, 58, 66, 70, and 83 were associated with persistent infections [31]. This was a very important observation since it is a persistent infection with hrHPV that is associated with cervical cancers. Most of the infections that were persistent were from hrHPV genotypes covered in the bivalent vaccine.

The first study to report HPV genotypes from two anatomical sites from one individual was by Dube Mandishora and colleagues in 2017. They detected HPV genotypes using next-generation sequencing from duplicate cervicovaginal and anal swabs of 144 women attending routine cervical cancer screening at a tertiary hospital in Harare [37]. From both anatomical sites, HPV 18 (21%), 52 (21%), and 16 (19%) were the most common, differing in order of highest frequency. HPV 35 was among the genotypes detected in the cervicovaginal swabs but not in the anal swabs.

Our search managed to retrieve only two studies that focused on Zimbabwean rural areas. The first study published in 2004 enrolled 235 women from Mupfure, a north-western rural farming area, and GP5+/6+ polymerase chain reaction (PCR) was used for HPV detection. In this study, the frequent hrHPV genotypes in their decreasing frequencies were HPV 35, 58, 33, 45, 18, 56, and 16 [29]. The lrHPV genotypes in their descending frequency were 54, 11, and 6. Another study sampled cervicovaginal swabs in Zimbabwean women from rural Hurungwe, Mashonaland, West Province from January to May 2017. The most common HPV genotypes were HPV 35, 18, 52, 68, 16, 58, 45, 56, and 51 in their decreasing frequency [40]. Although most participants did not have cervical malignancies, the data contributed to knowledge of the HPV genotypes in circulation in women residing in a non-urban area. There is still a wide knowledge gap on the distribution of HPV genotypes in Zimbabwean rural areas.

With the rise in anal cancers [51], there is a need to generate more information on the distribution of HPV genotypes in the anal canal thereby helping in policy formulation. The only two available studies have been done in Harare, and there are no data on the anal HPV distribution from other provinces of Zimbabwe. One study conducted in the period of 2014–2015 found an anal HPV prevalence of 20% and 60% in HIV-infected men and women, respectively [39]. HPV testing was performed using MY09/MY11 PCR, followed by typing using the dot blot method. Generally, the most common hrHPV genotypes in their decreasing frequencies were 58 (13%), 31 (11%), 16 (9%), 18 (2.5%), and lrHPV 11 (17%) and 53 (11%). When stratified by gender, HPV 16, 31, 35, 68, 58, and 66 were identified in men and HPV 16, 18, 31, 33, 45, 51, 56, 68, 58, 59, 6, 63, and 111 in women [39]. Another study detected HPV genotypes using next-generation sequencing from anal swabs of 144 women attending routine cervical cancer screening at Parirenyatwa VIA clinic in Harare [37]. The most common anal hrHPV genotypes were 52 (19%), 18 (17%), and 16 (16%) in their decreasing frequencies. Although less frequent, HPV 6, 11, 31, 33, and 58 were also detected from anal swabs of these women. The few studies described above demonstrate that HPV 16 and 18, included in the bivalent vaccine, are among the most common anal HPV genotypes. The nonavalent vaccine includes the remaining prevalent anal HPV genotypes. However, there is a need for more studies on anal HPV genotypes to be conducted in histologically confirmed cancers and from more provinces of Zimbabwe.

Distribution of HPV Genotypes in Histologically Confirmed Cancers

There are limited data on the distribution of HPV genotypes in histologically confirmed cancer cases in Zimbabwe. The first study in Zimbabwe to report HPV genotypes singly from women with cervical cancer was done in Harare from 43 women with cervical cancer in 2003 [27]. HPV detection was done by means of

degenerate primers in a nested PCR and genotyping of HPVs by restriction fragment length polymorphism analysis. The most frequent HPV genotypes identified in the invasive squamous cell carcinoma samples were 16 (59%), 33 (31%), 18 (14%), and 31 (2%).

In 2003, a subsequent study from 98 Zimbabwean women with invasive cervical cancer identified HPV 16 (61%), 33 (39%), 18 (18%), and 31 (4%) as the most frequent genotypes, and one case each of HPV 35 and 58 was also detected [28]. Nested PCR was used for amplification of HPV-DNA and restriction fragment length polymorphism to characterise the HPV genotypes.

A recent study stratified HPV genotypes by HIV status in 107 women with invasive cervical carcinoma from 4 urban referral hospitals in Zimbabwe from June 2014 to December 2015. HPV 16 (67.9%), 18 (43.4%), 56 (18.9%), 45 (15.1%), 33 (11.3%), and 58 (9.4%) were identified in HIV-infected women in their decreasing frequencies. HPV 16 (81.5%), 18 (24%), 33 (13%), 35 (11%), 56 (9%), and 45 (7.4%), in their decreasing frequencies, were identified in HIV-uninfected women [38]. HPV testing was performed using MY09/MY11 PCR followed by genotyping using dot blot hybridisation. In this study, 83% of the cases could be prevented by the bivalent vaccine as HPV 16 and 18 were found in women of that proportion. hrHPV genotypes not covered by the bivalent vaccine were also common in these studies and HPV 35, which is not yet included in the available vaccines was also detected.

Another recent study recruited 258 women with histologically confirmed invasive cervical cancer diagnosis between July 2016 and January 2019 from an outpatient oncology facility, Parirenyatwa Group of Hospitals Radiotherapy and Chemotherapy Centre (RTC), in Harare, Zimbabwe [3]. hrHPV subtypes were genotyped using a clinically validated Anyplex™ II HPV HR detection kit (Seegene, Seoul, South Korea). HPV16 (48%) was the most prevalent genotype, followed by HPV35 (26%), HPV18 (25%), HPV58 (11%), and HPV33 (10%). The study also found that one-third of the participants haboured single HPV infection with HPV16 (41%), HPV18 (21%), and HPV35 (21%) being the most prevalent. At the time of this review, there were no published data on the distribution of HPV genotypes in HPV-related cancer other than cervical cancer.

Distribution of HPV Genotypes in Benign Conditions

There are only two studies that have been done in Zimbabwe to determine the distribution of HPV genotypes in benign diseases. In the first study, samples from 52 children with RRP were tested for HPV using PCR and genotyped for next-generation sequencing. HPV 6 and 11 constituted 85% of the infections and HPV 16/18 in 15% of the cases with HPV 33, 35, and 58 only found in co-infection cases [7]. This study concluded that since HPV 6 and 11 were the predominant types causing RRP, the bivalent vaccine could not protect these children against HPV-related RRP. Quadrivalent or nonavalent vaccines are the appropriate vaccine choices.

The second recent study sampled 100 women with genital warts (condyloma accuminata) in Harare, and HPV-DNA testing and typing was done by Southern Dot Blot Hybridisation [41]. The lrHPVs were the most prevalent, accounting for 86% of the cases. The most prevalent genotypes in their decreasing frequencies were lrHPV 11(47%), 6 (42%), and hrHPV 16 (14%). The quadrivalent vaccine would be more appropriate to include coverage for the most common genotypes (HPV 6 and 11) that cause the majority of these cases of condyloma accuminata.

Discussion

In Zimbabwe, the current HPV vaccination program is utilising the bivalent vaccine in prepubescent girls. While this strategy is important for the prevention of most cervical cancer cases, consideration of expansion of the programme to include boys as well as the inclusion of the quadrivalent or nonavalent vaccine is warranted to fully address other HPV-related diseases in Zimbabwe.

From the studies that we reviewed, HPV 16/18 causes 83% of cervical cancers and 14% of anogenital warts in Zimbabwe [7, 38, 41]. While the bivalent vaccine has proven efficacy in the prevention of incident and persistent cervical infections with HPV 16 and 18, assuming perfect vaccine coverage, the bivalent vaccine would only possibly prevent 83% of cervical cancer cases and 14% of anogenital wart (condyloma accuminata) cases in Zimbabwe [8, 52–54]. From the distribution of HPV genotypes in the anal canal, the bivalent vaccine could protect against most anal canal HPV infections.

In Zimbabwe, as with many African countries such as Zambia, Uganda, and Malawi, HPV genotypes other than HPV 16 and 18 were common in HPV-related diseases of the head and neck and anogenital regions [10, 55–59]. Furthermore, a study in Zimbabwe found that 69% of the rural women had at least one of the 12 hrHPV types not present in the bivalent vaccine in their cervicovaginal tract. Additionally, a third of the women with positive

cytology for intraepithelial lesions had hrHPV genotypes not covered by the bivalent vaccine [40]. This suggests that women in these regions will remain at risk even if they receive the bivalent vaccine.

While the bivalent vaccine can offer cross-protection against other HPV genotypes, it is inadequate to cover the genotypes found frequently in Zimbabwe. In a Dutch population, the bivalent vaccines could offer cross-protection only against HPV 31/35/45/52 [53]. In a study in Scotland, the bivalent vaccine was proven to offer cross-protection against HPV 31/33/45 [60]. Cross-protection with HPV bivalent vaccine was not found in HPV 35, 39, 51, 52, 56, 58, 59, and 68. Most of these genotypes that showed non-cross-protection are prevalent in the Zimbabwean setting. As a result, many of the prevalent genotypes in Zimbabwe would not be expected to be covered even by cross-protection of the available bivalent vaccine. Most studies have also demonstrated the inadequacy of the cross-protection of the bivalent vaccine in protecting against most genotypes not covered by the vaccine [52, 61–64].

Another critical factor to consider is the vaccine's ability to provide protection against other HPV-related diseases, such as head and neck cancers. In these diseases, males are more commonly affected than females, and HPV types other than 16 and 18 are common. Therefore, there is a need to reconsider the inclusion criteria for the candidates for the vaccination program to include males and females. Furthermore, the high prevalence of HPV genotypes not included in the bivalent vaccine warrants the inclusion of the quadrivalent or nonavalent vaccine and consideration of HPV 35 in future vaccine development since HPV 35 is not covered in any of the currently available vaccines. This genotype was identified in Zimbabwe in cervical cancer cases, RRP, as well as anal anatomical sites in high frequency. This shows that if cross-protection does not occur, people will remain at risk of diseases caused by HPV 35 infection.

The lrHPV-related conditions in Zimbabwe are not prevented by the bivalent vaccine. If a balance is to be struck on the prevention of most HPV-related conditions and the cost of the vaccine, the quadrivalent vaccine would be a preferred option in Zimbabwe. Based on the distribution of HPV genotypes, the nonavalent vaccine is the most appropriate vaccine choice for the Zimbabwean setting as it covers the most common lrHPV and hrHPV genotypes associated with diseases in Zimbabwe. In countries like Scotland, the vaccine was introduced together with a national surveillance programme designed to determine the longitudinal effects of vaccination on HPV infection at a population level [60, 65]. This may entail running a population-based baseline assessment where common HPV genotypes are determined at a population level in HPV-related diseases prior to the introduction of the vaccine. The best choice of vaccine will be made guided by national surveillance and then the vaccine introduced as an intervention and successive evaluation surveys performed afterwards for impact assessment. The impact assessment surveys will also help in understanding the issues of herd immunity and selective pressure on genotypes not included in the available bivalent vaccine.

Some of the laboratory methods for HPV genotyping used in the studies used in this review have low specificity. In situ hybridisation and immunohistochemistry and MY9/11 PCR have a specificity of 33.4% and 38.7%, respectively, despite having high sensitivity. This shows that in those two studies that used these methods, there was a possible misinterpretation of HPV genotypes. Sensitivity and specificity should always merit each other to provide a holistic picture of a diagnostic test. MY09/11 PCR lacks specificity for oncogenic HPV genotypes and studies recommend the use of type-specific multiplex PCR in clinical settings as a reliable tool for HPV genotyping [57]. Additionally, for methods that use MY9/11 PCR, the specificity can be increased by using HPV genotype identification methods like next-generation sequencing [37]. To increase specificity for in situ hybridisation and immunohistochemistry, most test platforms utilise hrHPV DNA in situ hybridisation as a second-tier test in p16-positive cases [62]. However, this two-tier testing is not available in all testing platforms, lacks optimal reproducibility, and slows turnaround time.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Authors Takudzwa Marembo, Racheal S. Dube Mandishora, and Megan Burke Fitzpatrick contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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