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Review

HPV Infection in Sub-Saharan Africa: Circulating Genotypes, Vaccination Strategies (Single-Dose Versus Two-Dose), and Implications of HIV Co-Infection

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Abstract

Cervical cancer is a major cause of morbidity and mortality among women in sub-Saharan Africa, where vaccination coverage remains below the World Health Organization target of 90% of girls fully vaccinated by 15 years of age. This narrative review synthesizes evidence on human papillomavirus (HPV) genotype distribution, single-dose versus two-dose vaccination, and the implications of human immunodeficiency virus (HIV) co-infection. Although HPV 16 and HPV 18 remain the predominant oncogenic types, HPV 35, HPV 52, HPV 45, HPV 33, and HPV 58 are reported frequently in sub-Saharan African populations. Consequently, some high-risk infections fall outside bivalent and quadrivalent vaccine coverage, and some detected types remain outside nonavalent vaccine coverage. Randomized trials in Tanzania and Kenya demonstrate durable single-dose immunogenicity through 60 months and vaccine efficacy above 98% against persistent vaccine-type infection through 54 months, respectively. A trial in Costa Rica provides a direct five-year randomized comparison showing non-inferiority of one dose to two doses. Equivalent single-dose efficacy and durability evidence for people living with HIV remains unavailable. These findings support expanded single-dose vaccination in immunocompetent populations alongside multidose pathways for people living with HIV, genotype-specific surveillance, and continued cervical screening.

Keywords: human papillomavirus; cervical cancer; sub-Saharan Africa; HPV genotypes; HPV vaccination; single-dose vaccine; HIV–HPV co-infection; vaccine effectiveness; cervical-cancer screening; immunogenicity

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1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) worldwide, and persistent infection with oncogenic HPV genotypes is a necessary cause of invasive cervical cancer [1]. Cervical cancer was the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women globally in 2024, with an estimated 604,196 new cases and 279,583 deaths [2].

The distribution of that burden is highly uneven. WHO has projected that, without acceleration of prevention efforts, cervical cancer will continue to kill several hundred thousand women each year, with the large majority of deaths occurring in low- and middle-income countries (LMICs) and a disproportionate share in sub-Saharan Africa (SSA) [3].

HPV is transmitted principally through sexual contact. Microabrasions of the genital epithelium allow virions to access the basal layer of the squamous epithelium, where

infection of proliferating basal keratinocytes is required for a productive and potentially persistent infection [4]. Most infections are transient and are cleared by the host immune response; a minority persist, and, in a small subset, persistent infection with a high-risk (HR) genotype drives progression through cervical intraepithelial neoplasia (CIN) to invasive disease over years to decades [1].

Two developments make a sub-Saharan-Africa-focused synthesis timely. First, in December 2022, WHO recommended one- or two-dose schedules for immunocompetent individuals aged 9–20 years, with girls aged 9–14 years as the primary target population; the single-dose option is an alternative, off-label public-health recommendation. Immunocompromised individuals, including people living with HIV (PLHIV), should receive at least two doses and, where possible, three [5]. Second, an expanding body of SSA pooled analyses and studies from several countries indicates that some HR types reported in the region are not included in the vaccine formulations most widely used [6–9]. These two observations pull in different directions: dose reduction improves reach and affordability, while genotype diversity argues for broader valency. Reconciling them requires region-specific evidence.

This review therefore aims to (1) synthesize the reported distribution of circulating HPV genotypes across SSA; (2) evaluate evidence comparing single-dose and two-dose HPV vaccination, with particular emphasis on trials conducted in SSA populations; and (3) assess the implications of HIV co-infection for HPV natural history, genotype distribution, and vaccine response. Evidence from outside SSA is included where it provides essential comparative evidence on vaccine dosing, immunogenicity, or long-term effectiveness. We also identify research gaps that investigators and research networks in SSA are well positioned to address.

2. Review Approach

This was a narrative review, and no protocol was registered. Sources were identified through searches of PubMed/MEDLINE and ClinicalTrials.gov, the websites of WHO, IARC, and Gavi, and the reference lists of included trials and reviews. Searches combined terms for HPV (human papillomavirus, HPV), genotype (genotype, type distribution), vaccination (vaccine, single dose, one dose, dose reduction, immunobridging), HIV (HIV, people living with HIV), and region (sub-Saharan Africa, Africa, and individual country names). Literature published up to 30 September 2026 in English was considered.

Sources were eligible if they addressed at least one of the review's three objectives and were peer-reviewed primary studies, randomized trials, observational cohorts, systematic reviews, meta-analyses, modeling or costing studies, or current guidance or surveillance reports from WHO, IARC, or Gavi. Priority was given to primary data from SSA and to studies measuring vaccine efficacy, comparing dose schedules, or comparing vaccine-induced antibody responses with those in groups in which protection has already been demonstrated (immunobridging). Studies conducted outside SSA were included when they provided essential comparative evidence on dose schedules, immunogenicity, efficacy, or long-term effectiveness. Conference abstracts, case reports, and studies without type-specific or dose-specific data were excluded. The criteria for the summary tables were as follows. Table 1 includes SSA studies and syntheses that reported genotype-specific high-risk HPV data and described the specimen and assay used, selected to span the main population types (adolescent girls and young women, screening populations, and women living with HIV) and subregions. Table 1 is grouped by population type because prevalence differs markedly with age, HIV status, and recruitment setting, and the rows illustrate the range of evidence rather than comparable estimates. Despite this heterogeneity, the same non-16/18 types recur: HPV 52 was among the most frequent high-risk types in seven

of the eight studies and syntheses, and HPV 35 and HPV 58 in six each, across all three population groups.

Table 2 includes all randomized trials identified that compared, or were designed to inform, single-dose versus multidose vaccination, together with the two long-term cohorts that first suggested single-dose protection. Table 3 includes SSA studies that reported HPV prevalence or genotype distribution among women living with HIV or by HIV status, together with modeled estimates of HIV-attributable cervical cancer.

Because the review was narrative, records screened and excluded were not logged, and the number of records identified at the search stage cannot be reported; in total, 86 sources are cited. No duplicate screening, formal risk-of-bias assessment, or quantitative synthesis was undertaken, so selection bias cannot be excluded. To limit it, evidence that qualified or ran counter to the review's conclusions was deliberately retained, including immunogenicity end points that did not meet prespecified non-inferiority criteria, an analysis that found no single-dose cross-protection, and studies reporting stakeholder hesitancy about single-dose schedules. The principal conclusions were also checked for consistency with independent systematic reviews and guideline evidence reviews of single-dose vaccination [5,10], vaccine responses in PLHIV [11,12], and genotype distribution in African women [8,13]. Findings are therefore presented as a critical narrative synthesis of a heterogeneous evidence base.

Table 1. Summary of selected studies and evidence syntheses reporting HPV epidemiology in sub-Saharan African populations, grouped by population type.

Country/Setting	Study Population	HIV Status	Specimen and Assay	HPV Prevalence	Most Frequent High-Risk Genotypes	Ref.
Adolescent girls and young women						
South Africa, KwaZulu-Natal	Prospective cohort, women aged 14–30 years; n = 224	Negative	Cervicovaginal lavage; Roche Linear Array	Any HPV 76.3% (171/224; 95% CI 70.8–81.9); HR 54.5% (122/224)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58	[14]
South Africa, Cape Town and Soweto	Unvaccinated women aged 16–22 years; 291 valid results	Negative	Endocervical samples; Roche Linear Array	Any HPV 66.7% (194/291); HR 45.7% (133/291)	16, 18, 51, 58	[15]
Tanzania, Mwanza	Secondary-school girls aged 17–18 years; 385 valid results	Tested; ~1% positive	Vaginal swabs; Roche Linear Array	Any HPV 32.5% (125/385); HR 18.2% (70/385)	16, 39, 52, 58, 68	[16]
Screening and community populations						
Zimbabwe, rural Hurungwe	Women aged 30–65 years; 643 valid results	Mixed (123 positive; 520 negative)	Self-collected cervicovaginal specimens; GeneXpert with extended genotyping	HR 17.4% (112/643); HIV-positive 33.3% (41/123); HIV-negative 13.7% (71/520)	16, 18, 35, 51, 52, 58, 68	[6]
Zimbabwe, Karanda Mission Hospital, Mt Darwin	Women attending cervical screening; n = 400	Mixed	Clinician-collected cervical specimens; GeneXpert, then Anyplex II HPV28	HR 20.8% (83/400)	35, 45, 52, 58, 68	[17]
Ethiopia, three eastern hospitals	Women attending screening; 886 valid results	Not reported	Cervical samples; Anyplex II HPV HR	HR 12.4% (110/886)	16, 31, 35, 52, 58	[18]
Burundi, urban and rural	Women stratified by HIV status and residence; n = 600	Stratified (301 positive; 299 negative)	Cervical specimens; RIATOL qPCR (urban), nested PCR (rural)	Any HPV: urban HIV-positive 45.7% (69/151); urban HIV-negative 13.4% (20/149); rural HIV-positive 30.0% (45/150); rural HIV-negative 31.3% (47/150)	16, 18, 35, 45, 51, 52, 56, 66	[19]
Women living with HIV						
Kenya	Systematic review and meta-analysis	Positive	Cervical specimens; assays varied	Pooled HR or potentially HR HPV 64% (95% CI 50–77)	16, 18, 35, 52	[20]

HPV, human papillomavirus; HIV, human immunodeficiency virus; HR, high-risk; CI, confidence interval. Risk classifications follow the individual studies. These estimates describe different populations and should not be treated as directly comparable national prevalence estimates. Rows are grouped by population type because prevalence varies with age, HIV status, and recruitment setting; the table illustrates the range of available evidence and is not intended for comparison between rows.

Table 2. Key trials and cohorts comparing single-dose with multidose HPV vaccination: design, population, vaccine, follow-up duration, and principal immunogenicity or efficacy findings.

Study (Country)	Design	Population (Age; HIV Status)	Vaccine	Follow-Up	End Point	Key Finding	Key Limitation
DoRIS (Tanzania) [21,22]	Open-label RCT: one vs. two vs. three doses	930 girls, 9–14 y; HIV-negative (tested)	2vHPV, 9vHPV	24 and 60 mo	Serological	HPV 16 NI met; HPV 18 NI not met, although seropositivity > 98% at 24 mo and 93–98% at 60 mo; GMCs stable from 12 to 60 mo	No clinical end point
DoRIS multiplex substudy [23]	RCT substudy: one vs. two doses	9vHPV arms of DoRIS; HIV-negative	9vHPV	36 mo	Serological	After one dose, 100% seropositive for HPV 16, 31, 58; 73.0–87.7% for HPV 6, 45, 52 (98.6% for HPV 45, 52 after two doses)	No clinical end point; clinical relevance of lower seropositivity unknown
DoRIS vs. CVT and IARC India [24]	Immunobridging	DoRIS vs. single-dose recipients in efficacy cohorts	2vHPV; 9vHPV vs. 4vHPV	24 mo	Serological, bridged to efficacy	HPV 16 and HPV 18 GMCs non-inferior	Historical, non-randomized comparators; different vaccine in India comparison
DoRIS vs. KEN SHE [25]	Immunobridging	Girls 9–14 y vs. women 15–20 y; HIV-negative	2vHPV, 9vHPV	24 mo	Serological, bridged to efficacy	GMC ratios non-inferior (0.90–1.47)	Cross-trial comparison; assumes antibody level predicts protection
KEN SHE (Kenya) [26–28]	Double-blind RCT vs. meningococcal vaccine	2275 women, 15–20 y; HIV-negative (tested)	2vHPV, 9vHPV	18, 36, and 54 mo	Virological	VE against persistent HPV 16/18: 97.5% (18 mo), 97.5–98.8% (36 mo), 99.3% (54 mo)	No concurrent multidose arm; 54-mo estimate after control cross-over; older than target age
ESCUDDO (Costa Rica) [29,30]	Double-blind RCT: one vs. two doses, plus unvaccinated survey	20,330 girls, 12–16 y; HIV status not reported	2vHPV, 9vHPV	5 y	Virological	One dose NI to two doses against persistent HPV 16/18; VE ≥ 97% in all four groups	Non-SSA setting with different genotype distribution; VE estimated against a non-randomized survey
CVT (Costa Rica) [31,32]	Post-hoc analysis of RCT	Women 18–25 y; HIV status not reported	2vHPV	Up to 16 y	Virological and serological	Sustained protection against HPV 16/18; single-dose seropositivity 99.4% (HPV 16) and 98.8% (HPV 18) at 16 y	Dose groups not randomized; small single-dose group
IARC India cohort [33,34]	Prospective cohort after interrupted randomization	Girls 10–18 y; HIV status not reported	4vHPV	10 y; median 12 y	Virological	Single-dose VE against persistent HPV 16/18 95.4% (10 y) and 92.0% (median 12 y), comparable to two and three doses	Dose groups not randomized; unvaccinated comparators recruited separately

Table 3. Summary of HIV–HPV co-infection studies in sub-Saharan African populations: setting, population, HPV prevalence by HIV status, predominant genotypes, and reported cervical outcomes.

Setting	Population (n; HIV Status)	hrHPV Prevalence	Predominant High-Risk Types	Key Cervical Outcome	Ref.
Harare, Zimbabwe	2725 WLHIV with valid results; long ART duration, mostly virally suppressed	53% (95% CI 51–55)	58, 52, 35, 16	High hrHPV prevalence despite viral suppression	[35]
Harare, Zimbabwe	321 WLHIV; 2-year follow-up	24.9%; 65% of positives with types other than 16 or 18/45	Non-16/18/45 types	Incident cervical disease only in hrHPV-positive women (6.41 per 100 person-years; 95% CI 3.33–12.32); VIA-positive IRR 12.57 (95% CI 4.14–38.19)	[36]
Mt Darwin, Zimbabwe	400 women attending screening; mixed HIV status	27% (HIV-positive) vs. 15% (HIV-negative)	35, 45, 52, 58, 68	47% of hrHPV-positive women had a single type not covered by 9vHPV	[17]
Burundi, urban and rural	600 women; 301 HIV-positive, 299 HIV-negative	Highest in urban HIV-positive women	Urban HIV-positive: 52, 51, 56, 18, 16	HPV and HIV independently associated with cervical lesions	[19]
Kenya (pooled)	WLHIV; systematic review and meta-analysis	64% (95% CI 50–77), HR or potentially HR	Abnormal cytology: 16, 35, 52	Shift toward non-16/18 types in abnormal cytology	[20]
Harare, Zimbabwe (ZIMGARD)	98 adolescents and young adults with perinatally acquired HIV, mean 6 years after 4vHPV	Any HPV 69%; high-risk types only 17%	45, 56, 58, 52, 18	Cross-sectional; cannot distinguish vaccine failure, post-vaccination acquisition, or prior infection	[37]
SSA (modeled)	Population-level estimates	Not applicable	Not applicable	24.9% of cervical cancers in WLHIV; 20.4% attributable to HIV; 86% among women aged ≤34 years in Southern Africa	[38]
Global (modeled)	Population-level estimates	Not applicable	Not applicable	5.8% of cervical cancers attributable to HIV; approximately sixfold risk in WLHIV	[39]

4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; ART, antiretroviral therapy; hrHPV, high-risk HPV; SSA, sub-Saharan Africa; VIA, visual inspection with acetic acid; WLHIV, women living with HIV; IRR, incidence rate ratio.

3. HPV Biology and Pathogenesis

3.1. Classification

HPVs are small, non-enveloped, double-stranded DNA viruses of the family *Papillomaviridae*. More than 200 HPV types have been characterized and are assigned to five genera, of which alpha, beta, gamma, mu, and nu contain the human types [4]. Members of the *Alphapapillomavirus* genus include the HPV types established as causes of cervical cancer [1].

Genotypes are conventionally divided into HR and low-risk (LR) groups on the basis of epidemiological association with cervical cancer rather than on phylogeny alone. In the 2003 pooled analysis that established an epidemiological classification, 15 types were categorized as high-risk: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [40]. LR types are most often implicated in anogenital warts and recurrent respiratory papillomatosis, whereas HR types are associated with carcinomas of the cervix, vulva, vagina, penis, anus, and oropharynx [1].

3.2. Infection and the Viral Life Cycle

Infection is initiated when virions reach basal keratinocytes through microwounds or at transformation zones where the epithelium is thin, such as the cervical squamocolumnar junction [4]. Following entry, the viral genome is maintained at low copy number as an episome in the basal compartment. Productive viral replication and capsid assembly are

coupled to keratinocyte differentiation, so that virion production is confined to the superficial epithelial layers [41]. Because the infectious cycle is intraepithelial, involves minimal cell lysis, and produces no viremia, it generates only limited innate immune activation, which contributes to a modest and slowly developing natural antibody response [41].

3.3. From Persistent Infection to Invasive Cancer

Approximately 90% of HPV infections become undetectable within one to two years [1]. Persistence of an HR infection is the key intermediate step toward neoplasia. In persistent infection, deregulated *E6/E7* expression—often, but not invariably, associated with integration of viral DNA into the host genome and loss of E2-mediated control—drives degradation of p53 and inactivation of retinoblastoma protein, genomic instability, and clonal expansion [1,4]. Histologically, this progresses through CIN2 and CIN3, which are often grouped analytically as CIN2+, with CIN3 representing the immediate precursor of invasive carcinoma. The two phases differ in pace: CIN3 can arise within a few years of a persistent infection, whereas progression from CIN3 to invasive carcinoma typically takes a decade or longer. This prolonged, detectable precancerous phase is what makes screening effective [1].

Two features of HPV biology underpin the vaccine evidence reviewed in later sections. First, because infection requires access to basal keratinocytes through microtrauma and the infectious cycle produces no viremia, natural infection induces only weak antibody responses. By contrast, vaccine-induced serum neutralizing IgG reaches the genital tract by transudation into cervicovaginal mucus and by exudation at sites of epithelial trauma, where it blocks infection before it is established [42]. This explains why the vaccines prevent new infection but do not clear established infection, and why antibody concentration is used for immunobridging even though no correlate of protection has been defined. Second, the interval of years to decades between persistent infection and invasive cancer explains why vaccine trials use persistent infection as their end point, why the follow-up periods discussed in Section 6 are short relative to carcinogenesis, and why screening remains necessary in vaccinated cohorts.

3.4. The Cervicovaginal Microbiome

Evidence suggests that the composition of the cervicovaginal microbiome modifies HPV persistence. *Lactobacillus*-dominant communities are associated with more rapid clearance, whereas depletion of *Lactobacillus* species, higher bacterial diversity, and communities in which *Lactobacillus iners* or anaerobic taxa predominate are associated with prevalent HPV infection, delayed clearance, and higher-grade lesions [43]. In a longitudinal analysis, microbiome features were associated with the natural history of HPV infection independently of baseline cytology [43]. These associations are largely observational, and directionality remains incompletely resolved: dysbiosis may facilitate persistence, HPV infection may alter the microbial community, or both may share upstream determinants. Data from SSA cohorts are limited, which is a notable gap given that bacterial vaginosis has been associated with prevalent HPV infection in SSA study populations [15].

3.5. Disease Spectrum Beyond Cervical Cancer

HPV contributes to a wider disease spectrum. LR types 6 and 11 cause the majority of anogenital warts. HR types, predominantly HPV 16, are implicated in a substantial fraction of anal, vulvar, vaginal, penile, and oropharyngeal cancers [1]. The attributable fraction varies by site and geography, and SSA data on non-cervical HPV-associated cancers remain sparse relative to cervical-cancer data. Because cervical cancer accounts for most of the HPV-attributable cancer burden in SSA women, the remainder of this review focuses

primarily on cervical disease while noting that vaccination and surveillance decisions have implications across all HPV-associated sites [1].

4. Epidemiology of HPV in Sub-Saharan Africa

4.1. Regional Patterns

Pooled analyses of women with normal cytology place Africa among the world regions with the highest HPV prevalence [44]. A systematic review and meta-analysis of African studies likewise reported higher pooled prevalence in women with neoplasia than in women with normal cytology [8]. More recent syntheses confirm these patterns while illustrating their heterogeneity. A 2022 meta-analysis of 27 studies from 19 SSA countries reported a pooled high-risk HPV prevalence of 34% (95% CI 29–39), higher in Southern Africa (53%) than in Eastern Africa (28%), with HPV 16 and HPV 52 the leading types in Eastern and Southern Africa and HPV 16 and HPV 35 in Western Africa [13]. A 2023 meta-analysis of 28 studies (22,652 participants) reported a pooled high-risk HPV prevalence of 75.5% among women living with HIV, with HPV 16, 35, 52, 18, and 45 the most frequent types [45]. Both combined women with different cytological and clinical status and reported very high heterogeneity, so neither replaces normal-cytology estimates. We identified no comparable updated all-age synthesis of women with normal cytology; the 2010 global analysis [44] and the 2015 African analysis [8] are therefore retained as prevaccination baselines. Reported estimates vary widely between and within countries, reflecting genuine epidemiological heterogeneity as well as differences in study population (community-based versus clinic-based), age structure, HIV prevalence, specimen type, and the analytical sensitivity and type coverage of the assay used. Comparisons across studies should therefore be interpreted with caution, and Table 1 reports assay and population characteristics alongside prevalence estimates.

HIV contributes substantially to cervical cancer burden, but its contribution varies across SSA subregions. In a model of cervical-cancer burden in 2020, the estimated fraction attributable to HIV was highest in Southern Africa (43.5%), followed by Eastern Africa (23.4%), Central Africa (10.0%), and Western Africa (8.9%) [38]. Figure 1 presents HPV prevalence and HIV-attributable cervical cancer as separate measures; these aggregated estimates do not establish that HIV explains subregional differences in HPV prevalence [8,38].

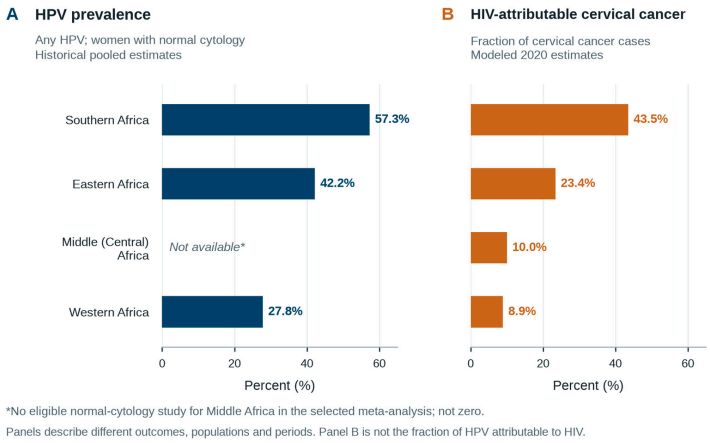


Figure 1. Regional HPV prevalence and HIV-attributable cervical cancer in sub-Saharan Africa. (**A**) Pooled prevalence of any HPV among women with normal cervical cytology, from Ogembo et al. [8], published in 2015. No eligible normal-cytology study from Middle Africa was included in that meta-analysis. (**B**) Modeled population-attributable fractions of incident cervical cancer due to HIV in 2020, from Ibrahim Khalil et al. [38]. The panels represent different outcomes, populations, and periods and should not be interpreted as a correlation or causal comparison.

Figure 1A shows that pooled HPV prevalence among women with normal cytology in the prevaccination period differed between SSA subregions, and that no eligible normal-cytology data were available for Middle Africa. Figure 1B shows that the modeled share of cervical cancer attributable to HIV differed more sharply, from 43.5% in Southern Africa to 8.9% in Western Africa. The two measures are shown together because both bear on where HIV-specific vaccination pathways matter most, not because one explains the other.

4.2. Age-Stratified Patterns

HPV prevalence in SSA populations peaks in adolescence and young adulthood. In a cohort of women aged ≤30 years in KwaZulu-Natal (median 21 years; IQR 18–23), HPV prevalence was 76.3%, with HPV 16, 18, 33, 35, 39, 45, 51, 52, 56, and 58 among the most frequently detected types [14]. Among unvaccinated, HIV-negative South African women aged 16–22 years, any HPV was detected in 66.7% (194/291) [15]. The authors interpreted their findings as supporting the introduction of the nonavalent vaccine and catch-up vaccination campaigns [15]. Such vaccination aims to prevent new infections with vaccine-targeted types not yet acquired, rather than clear infections already present [5,15]. In Tanzania, a decade of adolescent research documented high HPV prevalence and high incidence of new infection among sexually active girls, with rates exceeding those in older women [46].

Unlike in many high-income settings, several African studies do not show a marked decline in prevalence after the third decade of life. A second peak or a sustained plateau in older women has been reported and may reflect reactivation of latent infection, new acquisition, or reduced clearance in the context of HIV [8,20].

4.3. Behavioral and Structural Correlates

Early age at sexual debut, higher lifetime number of partners, concurrent or polygynous partnerships, non-cohabiting partnerships, other sexually transmitted infections (STIs), and bacterial vaginosis have all been associated with prevalent HPV in African study populations [14,15]. In a community-based study in rural Zimbabwe, however, several conventional risk markers, including age at first pregnancy, educational attainment, and oral contraceptive use, were not associated with HPV positivity, which the authors interpreted as consistent with near-ubiquitous community-level exposure [6]. These findings suggest that conventional risk markers may have limited discriminatory value in that setting; they should not be used alone to determine screening eligibility.

Structural determinants are at least as important as behavioral ones. Distance to health facilities, out-of-pocket costs, limited laboratory and cold-chain infrastructure, shortages of trained providers, and low awareness of HPV all constrain both screening and vaccination [47]. In one rural Zimbabwean survey, 81% of women had heard of cervical cancer but only 12% had heard of HPV, and only 5% had ever been screened [6].

5. HPV Genotype Distribution in Sub-Saharan Africa

5.1. Global Baseline

Globally, HPV 16 and HPV 18 together account for approximately 70% of invasive cervical cancers, with HPV 16 alone responsible for the largest single share [48]. HPV 31, 33, 45, 52, and 58, the five additional oncogenic types covered by the nonavalent vaccine, contribute a further estimated 12–20% [49]. Type distribution in women with normal cytology is broader and less dominated by HPV 16 than the distribution in cancer, reflecting differences in oncogenic potential between types [44,48].

5.2. Differential Distribution in Sub-Saharan African Populations

A consistent finding across African studies is a relatively larger contribution of non-16/18 high-risk types. In invasive-cervical-cancer specimens from SSA, HPV 16 and HPV 18 remained the most common types, but HPV 35 and HPV 45 were detected more frequently than in most other world regions [9]. Pooled African data similarly identify HPV 35, 52, 58, 45, and 33 among the most prevalent non-16/18 high-risk types [8]. This distinction between infection and cancer matters. In the largest multicountry study of histologically confirmed invasive cervical cancer from the region (570 cases from Ghana, Nigeria, and South Africa), the most common types among single-type infections were HPV 16 (51.2%), HPV 18 (17.2%), HPV 35 (8.7%), and HPV 45 (7.4%), whereas HPV 33 (4.0%) and HPV 52 (2.2%) were less common [9]. In South African cervical biopsies, HPV 35 was the second-most-common type among CIN3 lesions (22.2%) [50]. Cancer and precancer specimens therefore support a meaningful contribution of HPV 35 and HPV 45 to cervical disease in the region, whereas the prominence of HPV 52 and HPV 58 in screening populations does not appear to translate proportionally into invasive cancer.

HPV 35 has attracted particular attention. HPV 35 has been reported frequently in several African populations, including rural Zimbabwe [6]. Among Zimbabwean women living with HIV (WLHIV) attending routine screening in Harare (n = 2745), the most prevalent genotypes were HPV 58 (11%), HPV 52 (10%), HPV 35 (10%), and HPV 16 (9%) [35]. In a cross-sectional study of 240 Zimbabwean women with histologically confirmed cervical cancer, HPV 16 (35%), HPV 35 (33%), and HPV 18 (32%) were the most prevalent types [51]. At a rural mission hospital in northern Zimbabwe, 87 of 113 genotype detections (77%) classified as high-risk in the study were types not directly targeted by the bivalent or quadrivalent vaccines, including HPV 35, HPV 45, HPV 52, HPV 58, and HPV 68. Of the 113 detections, 53 (47%) were types not included in the nonavalent vaccine: HPV 35, HPV 39, HPV 51, HPV 53, HPV 56, HPV 66, HPV 68, HPV 69, and HPV 73 [17].

The significance of HPV 35 may not lie only in its frequency, although this evidence is less settled. In US cohorts, HPV 35 was more prevalent among African-American women than among women of other ethnicities (12.1% versus 5.1%) and accounted for a larger proportion of CIN3 cases as a single infection (5.5% versus 1.9%); however, among HPV-35-positive women, the risk of CIN3 or worse did not differ by ethnicity [7]. Viral genome analyses in the same study found a stronger association with precancer for the HPV 35 A2 sublineage in African-American women (odds ratio 5.6 versus the A1 sublineage, 95% CI 1.3–24.8), a higher frequency of A2 in invasive cancers from Africa than from other regions (41.9% versus 10.4%), and variants associated with precancer, including one in the *E7* oncogene [7]. These are associations. Neither the larger contribution of HPV 35 to CIN3 nor the sublineage and *E7* variant findings establish, in themselves, that HPV 35 has greater oncogenic potential in women of African ancestry, and this remains an open question.

Country- and region-specific patterns include the following. In Kenya, a systematic review and meta-analysis among HIV-positive women reported that HPV 16 was the most prevalent type in women with abnormal cytology (26%, 95% CI 23–30%), followed by HPV 35 (21%, 95% CI 18–25%) and HPV 52 (18%, 95% CI 15–21%); in invasive cervical cancer, the most prevalent types were HPV 16 (37%, 95% CI 28–47%) and HPV 18 (24%, 95% CI 16–33%) [20]. In Burundi, genotype distribution differed by both HIV status and urban or rural residence: among HIV-positive women in urban areas, the most common high-risk or probable high-risk types were HPV 52, 51, 56, 18, and 16, whereas among HIV-negative urban women, HPV 66, 67, 18, 45, and 39 predominated; in rural areas, HPV 66, 16, 18, and 33 predominated among HIV-positive women and HPV 16, 66, 18, 35, and 45 among HIV-negative women [19]. In Ethiopia, an opinion article synthesizing published genotype data reported HPV 16 in over 37% of HPV-positive women and HPV 18 in only 4.4%, with non-

16/18 high-risk types accounting for approximately 46% of high-risk infections [52]. South African data likewise show high prevalence of non-vaccine high-risk types in adolescents and young women [14,15].

5.3. Implications for Vaccine-Type Coverage

The bivalent HPV vaccines target HPV 16 and HPV 18, the quadrivalent vaccine additionally targets HPV 6 and HPV 11, and the nonavalent vaccine additionally targets HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58 [49,53]. In a rural Zimbabwean study, 69% of detected high-risk HPV genotypes were outside the HPV 16/18 targets of the bivalent vaccines, whereas 32% were outside the oncogenic types targeted by the nonavalent vaccine [6]. In Ethiopia, an analogous genotype-coverage analysis estimated that approximately 46% of detected high-risk HPV infections involved types not targeted by the quadrivalent vaccine [52].

These estimates describe genotype coverage, not vaccine effectiveness, and should not be read as predicted vaccine failure. Three qualifications matter. First, oncogenic potential differs markedly between types, so the proportion of infections covered is not the proportion of cancers averted; HPV 16 contributes disproportionately to cancer relative to its share of infections [48]. Second, some bivalent-vaccine studies have reported cross-protection against selected non-vaccine types, particularly HPV 31, 33, and 45; evidence for HPV 35 is less certain [54]. This evidence derives mainly from multidose schedules of the AS04-adjuvanted bivalent vaccine, and cross-protection is partial and can vary by viral variant [55]. Under a single-dose schedule, KEN SHE found no evidence of bivalent-vaccine cross-protection against persistent HPV 31/33/45 infection (vaccine efficacy 10.1%, 95% CI −38.7 to 41.7) [27], and a South African single-dose campaign showed no reduction in non-vaccine high-risk types [56]. Cross-protection should therefore not be assumed to offset valency gaps in single-dose programs, particularly for HPV 35. Third, most coverage analyses are based on prevalent infection in screening populations rather than on cancer specimens. Even allowing for these qualifications, broader-valency formulations may increase direct HPV type coverage in SSA settings, although their incremental cancer-prevention benefit requires cancer-weighted, country-specific evaluation. Continued cervical screening remains necessary in vaccinated cohorts [57].

6. HPV Vaccines: Products, Coverage, and Effectiveness

6.1. Available Products

WHO's 2024 product-choice guidance lists five WHO-prequalified HPV vaccines: Cervarix, Cecolin, and Walrinvax (bivalent); Gardasil (quadrivalent); and Gardasil 9 (nonavalent). Cervavac is nationally licensed but was not listed as WHO-prequalified in the guidance [53], although it has since been listed as WHO-prequalified with effect from 25 September 2026 [58]. All are virus-like-particle (VLP) vaccines based on the L1 major capsid protein, are prophylactic rather than therapeutic, and do not clear established infection [49]. Additional WHO-prequalified bivalent products manufactured outside the traditional supplier base have entered the market and are relevant to supply security and price in SSA [5]. Table 4 summarizes products, manufacturers, types covered, and current status relevant to African immunization programs.

Table 4. Prophylactic HPV vaccines: manufacturers, valency, targeted HPV types, WHO prequalification, procurement price, and use in sub-Saharan African programs.

Vaccine (Manufacturer)	Valency; HPV Types Targeted	WHO Prequalification	Gavi/UNICEF Availability	UNICEF Price per Dose, Gavi-Supported Countries (US$, 2026)	Use in SSA National Programs
Cervarix (GlaxoSmithKline, Rixensart, Belgium)	Bivalent; 16, 18	July 2009	Yes	5.18	Available to Gavi-supported programs; product use by country not publicly reported
Gardasil (Merck Sharp & Dohme LLC, Rahway, NJ, USA)	Quadrivalent; 6, 11, 16, 18	May 2009	Yes	4.50	Used in national programs, e.g., Rwanda (from 2011) and Nigeria (from 2023)
Gardasil 9 (Merck Sharp & Dohme LLC, Rahway, NJ, USA)	Nonavalent; 6, 11, 16, 18, 31, 33, 45, 52, 58	February 2018	Not in Gavi portfolio (2023)	No Gavi price; 13.50–33.50 for UNICEF-procuring middle-income countries (2025)	No national-program use identified; used in SSA trials (DoRIS, KEN SHE)
Cecolin (Xiamen Innovax Biotech Co., Ltd., Xiamen, China)	Bivalent; 16, 18	October 2021	Yes	2.90	Available to Gavi-supported programs; product use by country not publicly reported
Walrinvax (Yuxi Zerun Biotechnology Co., Ltd., Yuxi, China)	Bivalent; 16, 18	August 2024	Award status not confirmed	2.80	No national-program use identified
Cervavac (Serum Institute of India Pvt. Ltd., Pune, India)	Quadrivalent; 6, 11, 16, 18	September 2026	Not established	Not listed	No national-program use identified

All listed vaccines are non-live recombinant virus-like-particle vaccines and are prophylactic rather than therapeutic. WHO recommends a one- or two-dose schedule for girls aged 9–14 years and for girls and women aged 15–20 years, and two doses administered six months apart for women aged 21 years or older. Individuals known to be immunocompromised or living with HIV should receive at least two doses and, where feasible, three doses. WHO population-level recommendations may differ from the schedules authorized in individual product labels, and national licensure, procurement, and availability may vary. WHO prequalification dates are from WHO product-choice guidance and the WHO prequalification database. Prices are UNICEF Supply Division awarded prices per dose for Gavi-supported countries and apply to specific supply agreements and presentations. Cervarix contains the AS04 adjuvant (aluminum hydroxide and 3-O-desacyl-4′-monophosphoryl lipid A), which is relevant to the cross-protection data in Section 5.3; the other products contain aluminum-based adjuvants. 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; AS04, Adjuvant System 04. Sources: World Health Organization [53]; UNICEF Supply Division [59]; Gavi [60]; WHO prequalification database [58].

African national immunization programs use different HPV-vaccine products, and product availability and procurement are country-specific [53,61]. Zimbabwe introduced HPV vaccine nationally in 2018, following a Gavi-supported demonstration project [62,63]. Three points from Table 4 are relevant to SSA programs. Gavi-supported countries can procure two bivalent products and the quadrivalent product at US$2.90–5.18 per dose, whereas the nonavalent vaccine, the only product covering HPV 31, 33, 45, 52, and 58, was not in the Gavi portfolio and is substantially more expensive [59,60]. No licensed product covers HPV 35. Public sources do not report which product each SSA country uses, which limits product-level analysis of genotype coverage.

6.2. Program Introduction and Coverage

By the end of April 2026, 36 countries in the WHO African Region had introduced HPV vaccine, and 11 additional countries planned introduction by 2029. Because WHO

regional boundaries are not geographically identical to SSA, these figures are presented as regional program context rather than as an exact SSA estimate. HPV vaccination coverage in the WHO African Region was reported as 47% for 2024 [61,64].

Coverage varies substantially between countries and districts within countries. Post-introduction coverage surveys in three Zimbabwean districts illustrate both the achievable reach of school-based delivery and the loss between the first and second doses [62]. In England, high sustained coverage was associated with substantial reductions in CIN3 and cervical-cancer incidence [65]. These results come from high-income settings, and their magnitude should not be assumed to transfer directly to African programs with different coverage, genotype distribution, and HIV prevalence.

6.3. Barriers to Uptake

Systematic reviews from SSA identify recurring barriers: insufficient information about the vaccine among parents, adolescents, and health workers; concern about adverse events and about effects on fertility; cost and financing uncertainty; limited cold-chain and transport capacity; difficulty reaching out-of-school girls; and competing demands on health workers during campaign delivery [47]. Facilitators include school-based delivery, interministerial collaboration between health and education sectors, provider recommendation, community and religious leader engagement, and integration with other adolescent health services [47]. Delivery costs are non-trivial. In Zimbabwe's demonstration project, the mean financial cost per fully immunized girl was US$40.03 and the economic cost was US$91.19, with school-based delivery substantially cheaper per girl than facility or outreach delivery [62].

6.4. Two-Dose Schedule Evidence

The two-dose schedule for individuals aged 9–14 years was adopted after immunobridging studies showed that antibody responses to two doses in this age group were non-inferior to those after three doses in older adolescents and young women in whom efficacy had been demonstrated [5,66]. Long-term follow-up supports durability: two-dose recipients maintain seropositivity and antibody concentrations over years, with non-inferiority to three doses demonstrated for most vaccine types, although non-inferiority has not been met for every type in every comparison, notably HPV 18 in some analyses [66]. Wider dosing intervals appear to yield antibody responses at least as high as those after a six-month interval [66].

Direct two-dose effectiveness data from African settings are limited. The DoRIS trial in Tanzania included two-dose arms and is the principal randomized source of two-dose immunogenicity data generated in Africa; at 36 months, two-dose Gardasil 9 recipients were seropositive for all nine vaccine types in almost all cases, including 98.6% seropositivity for HPV 45 and HPV 52 [21,23]. Population-level two-dose effectiveness studies in African cohorts are largely still in progress.

6.5. Single-Dose Schedule Evidence

Table 2 summarizes the principal trials and cohorts comparing single-dose with multi-dose HPV vaccination, together with their designs, populations, follow-up durations, and principal findings.

Follow-up is measured from initial vaccination. The KEN SHE 54-month estimates were derived from a time-varying Cox model after the delayed-control group received cross-over vaccination; they are not based on a continuously unvaccinated control group through month 54. Serological end points, antibody seropositivity or GMC; virological end points, incident persistent infection. HIV status is shown as reported in the trial publications or registrations. mo, months; NI, non-inferiority; RCT, randomized controlled trial; VE, vaccine

efficacy; y, years. 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; CI, confidence interval; CVT, Costa Rica Vaccine Trial; DoRIS, Dose Reduction Immunobridging and Safety Study; GMC, geometric mean concentration; IARC, International Agency for Research on Cancer; KEN SHE, Kenya Single-dose HPV-vaccine Efficacy study.

Read together, the studies in Table 2 provide complementary evidence of different kinds, each with its own limitations. DoRIS and the immunobridging analyses provide randomized serological evidence in the target age group but no clinical end points. KEN SHE provides randomized virological efficacy in an African population but no concurrent multidose HPV-vaccine arm. ESCUDDO provides the only direct randomized comparison of one and two doses, but in an immunocompetent Costa Rican population with a different genotype distribution. The long-term cohorts extend follow-up to 12–16 years but lack randomized dose groups, and none of the studies enrolled people living with HIV. Serological end points indicate immune response, whereas virological end points indicate protection against infection; Sections 6.5.2–6.5.4 and 6.6 interpret the findings with this distinction in mind.

6.5.1. Observational Foundations

Interest in a single dose grew from post-hoc analyses of two trials not designed to test dose reduction. In the Costa Rica Vaccine Trial (CVT), women who received a single dose of the bivalent vaccine maintained stable antibody concentrations and protection against HPV 16/18 infection for more than a decade [31]. In the International Agency for Research on Cancer (IARC) India cohort, in which randomization was interrupted, recipients of one, two, or three doses of the quadrivalent vaccine were followed for 10 years; vaccine efficacy against persistent HPV 16/18 infection after a single dose was comparable to that after two or three doses [33]. An updated systematic review of clinical-trial evidence concluded that a single dose appeared to offer comparable protection against HPV infection to two or three doses up to seven years after vaccination, while noting the observational and post-hoc nature of most data [10].

6.5.2. Randomized Evidence from Sub-Saharan Africa

Two randomized trials in African populations now anchor the evidence base.

The DoRIS trial (Dose Reduction Immunobridging and Safety Study, NCT02834637) randomized 930 HIV-negative Tanzanian schoolgirls aged 9–14 years in Mwanza to one, two, or three doses of the bivalent or the nonavalent vaccine. At 24 months, 99% of single-dose recipients of either vaccine were seropositive for HPV 16 IgG, meeting the prespecified non-inferiority criterion against two and three doses. Non-inferiority criteria for HPV 18 seropositivity were not met, although more than 98% of girls in all groups were HPV 18 seropositive. Antibody geometric mean concentrations (GMCs) after one dose were lower than those after two or three doses. Fifty-three serious adverse events occurred in 42 of 930 girls, most commonly hospital admission for malaria, with no events considered vaccine-related [21].

In the long-term extension to month 60, single-dose HPV 16 seropositivity exceeded 99% with either vaccine and remained non-inferior to two doses. HPV 18 seropositivity at month 60 was 98% in the one-dose bivalent group and 93% in the one-dose nonavalent group, and the non-inferiority criteria for HPV 18 were again not met. Single-dose HPV 16 and HPV 18 GMCs were lower than those after two doses but remained stable between month 12 and month 60, and there was no evidence of a difference in antibody avidity at month 36 [22]. Multiplex assessment of the nonavalent arms at month 36 showed all one-dose recipients seropositive for HPV 16, 31, and 58; 96.8–98.2% seropositive for HPV 11, 18, and 33; and 73.0–87.7% seropositive for HPV 6, 45, and 52, compared with 98.6%

for HPV 45 and 52 after two doses [23]. Participants are being followed for up to nine years [22].

The KEN SHE trial (NCT03675256) randomized 2275 Kenyan women aged 15–20 years to single-dose bivalent vaccine, single-dose nonavalent vaccine, or meningococcal vaccine as a control. At 18 months, vaccine efficacy against incident persistent HPV 16/18 infection was 97.5% for both HPV vaccines [26]. At three years, 75 incident persistent HPV 16/18 infections were detected in the modified intention-to-treat cohort: two in the bivalent group, one in the nonavalent group, and 72 in the control group; nonavalent efficacy was 98.8% (95% CI 91.3–99.8) and bivalent efficacy 97.5% (95% CI 90.0–99.4). Against the seven high-risk types covered by the nonavalent vaccine, efficacy was 95.5% (95% CI 89.0–98.2). No vaccine-related serious adverse events were reported [27].

DoRIS directly randomized girls to one-, two-, or three-dose schedules but evaluated immunogenicity rather than virological efficacy. KEN SHE evaluated single-dose efficacy against a meningococcal-vaccine control and did not include a concurrent multidose HPV arm.

6.5.3. Head-to-Head Randomized Comparison of One and Two Doses

The first randomized trial designed to compare one dose directly with two doses of the same vaccine has now reported. The ESCUDDO trial (NCT03180034) enrolled 20,330 girls aged 12–16 years in Costa Rica and randomly assigned them, double-blind, to one or two doses of the bivalent or the nonavalent vaccine; for ethical reasons, no placebo arm was included, and absolute vaccine effectiveness was estimated by comparison with a concurrent survey of unvaccinated girls and young women [29]. One dose met the prespecified criteria for non-inferiority to two doses against persistent HPV 16/18 infection for both vaccines, and effectiveness against HPV 16/18 infection relative to the unvaccinated survey population was at least 97% [30]. Long-term observational follow-up of the Costa Rica Vaccine Trial has separately shown HPV 16 and HPV 18 seropositivity of 99.4% and 98.8% among single-dose recipients 16 years after vaccination [32].

6.5.4. Immunobridging

Because efficacy end points are not obtainable in girls vaccinated before sexual debut within a feasible timeframe, immunobridging has been used to extend efficacy inferences to the target age group. Single-dose HPV 16 and HPV 18 GMCs at 24 months in DoRIS were non-inferior to those in single-dose recipients in CVT and the IARC India cohort: for the bivalent comparison, GMC ratios (DoRIS:CVT) were 1.30 (95% CI 1.00–1.68) for HPV 16 and 1.23 (95% CI 0.95–1.60) for HPV 18; for the nonavalent comparison against IARC India, ratios were 2.05 (95% CI 1.61–2.61) and 2.12 (95% CI 1.59–2.83), respectively [24]. In a subsequent analysis, month-24 GMCs in DoRIS were non-inferior to those in single-dose KEN SHE participants, in whom efficacy had been demonstrated: bivalent GMC ratios were 0.90 (95% CI 0.72–1.14) for HPV 16 and 1.02 (95% CI 0.78–1.33) for HPV 18, and nonavalent ratios were 1.44 (95% CI 1.14–1.82) and 1.47 (95% CI 1.13–1.90). Figure 2 presents these comparisons.

The interpretive limitation is important and is acknowledged by the trial investigators: there is no established immunological correlate of protection for HPV vaccines, so non-inferior antibody concentrations support but do not prove equivalent efficacy [24,25,66].

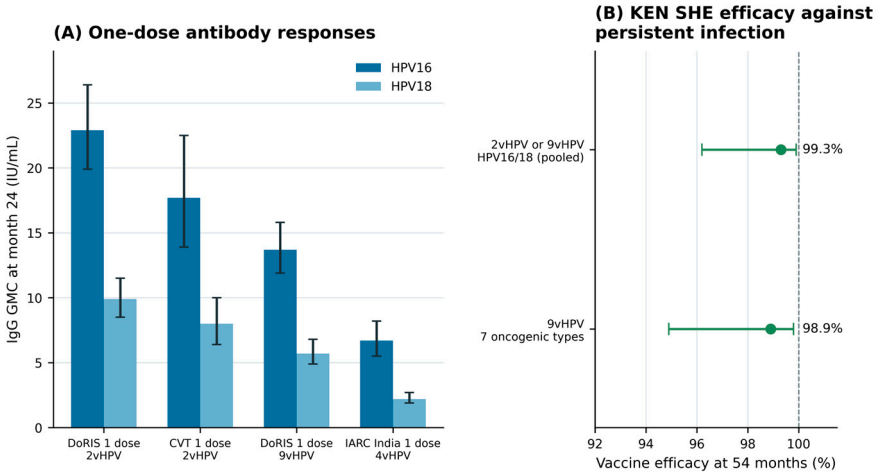


Figure 2. Single-dose HPV-vaccine immunogenicity and efficacy. (**A**) Month-24 serum HPV 16 and HPV 18 IgG geometric mean concentrations after one vaccine dose in the DoRIS, Costa Rica Vaccine Trial, and IARC India cohorts; error bars represent 95% confidence intervals. (**B**) KEN SHE vaccine efficacy at 54 months against incident persistent HPV 16/18 infection in the pooled bivalent and nonavalent groups and against the seven oncogenic vaccine types in the nonavalent group; error bars represent 95% confidence intervals. Sources: [24,28]. 2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; CI, confidence interval; CVT, Costa Rica Vaccine Trial; GMC, geometric mean concentration; IARC, International Agency for Research on Cancer.

6.5.5. Modeling and Cost-Effectiveness

Modeling analyses indicate that single-dose vaccination could avert a large proportion of the cervical cancers averted by two doses in LMIC settings, provided protection is sufficiently durable, and that the population-level benefit of reallocating doses to increase coverage can exceed the benefit of second doses to already-vaccinated girls [67,68]. Cost data support the same direction. In Tanzania, the financial cost per fully immunized girl was US$5.17 under a two-dose schedule and US$2.51 in a modeled single-dose scenario, with economic costs falling from US$23.34 to US$12.18 [69]. These are model-based or scenario-based estimates and are sensitive to assumptions about duration of protection. That sensitivity has been quantified. In a transmission-dynamic model calibrated to four LMICs, including Nigeria and Uganda, one-dose routine vaccination averted 69–94% of the cervical cancers averted by two doses under pessimistic assumptions of lower one-dose efficacy (85%) or a 30-year duration of protection, but only 35–69% if protection lasted 20 years; switching from one to two doses five years after program introduction recovered most of this loss (92–99%), and one dose required fewer doses per cancer prevented even with 20-year protection [67]. Because single-dose protection has shown no evidence of waning through 12–16 years of follow-up [32,34], the most pessimistic scenarios are not supported by current data, but they define the durability that long-term follow-up must confirm.

6.6. Implications of Dose Reduction for Sub-Saharan Africa

The programmatic case is strong. A single dose halves vaccine procurement volume in a supply-constrained market, removes the requirement to trace and revaccinate girls after 6–12 months, reduces service-delivery and cold-chain burden, and simplifies campaigns for out-of-school populations [69,70]. Stakeholder research across 19 LMICs found broad enthusiasm for single-dose schedules, motivated by anticipated gains in schedule completion and coverage and by savings for countries transitioning out of Gavi co-financing [70]. Among Kenyan health-care professionals, 76% considered a single-dose schedule accept-

able or very acceptable, with lack of information the main reason cited by those who were hesitant [71].

Three cautions temper this. First, long-term data from SSA populations remain limited relative to the decades over which cervical cancer develops. Randomized African follow-up now extends to five years for immunogenicity in the DoRIS trial and to 54 months for efficacy in the KEN SHE trial. At 54 months, single-dose vaccine efficacy against incident persistent HPV 16/18 infection was 99.3% (95% CI 96.2–99.9), while efficacy against persistent infection with the seven high-risk types included in the nonavalent vaccine was 98.9% (95% CI 94.9–99.8) [22,28]. Although these findings demonstrate high and durable protection over the observed period, longer follow-up remains necessary to establish protection across the timeframe relevant to cervical-cancer development. Longer follow-up from outside SSA is reassuring: single-dose antibody concentrations in the Costa Rica Vaccine Trial remained stable for 16 years [32], and, in the IARC India cohort, single-dose efficacy against persistent HPV 16/18 infection was 92.0% (95% CI 87.0–95.0) at a median of 12 years, with no HPV-16/18-associated high-grade precancer detected among vaccinated participants [34]. Persistent infection is an accepted surrogate end point for HPV-vaccine trials because cancer end points are not feasible [72], but it remains a surrogate. Second, HPV 18 antibody responses after a single dose did not meet the prespecified non-inferiority criterion in the DoRIS trial, although seropositivity remained high [21,22]. Separately, the ZIMGARD study raised a hypothesis concerning HPV 18 immunity, but its cross-sectional design cannot establish waning immunity or vaccine failure [37]. Because no correlate of protection has been established, these serological findings are best interpreted against populations in which single-dose efficacy has been demonstrated: DoRIS single-dose HPV 18 GMCs at month 24 were non-inferior to those of single-dose recipients in the Costa Rica Vaccine Trial, the IARC India cohort, and KEN SHE [24,25]. This concern is now partly, though not wholly, addressed: ESCUDDO found one dose non-inferior to two doses against persistent HPV 16/18 infection over five years, with vaccine effectiveness of at least 97% in every group, which suggests that lower HPV 18 antibody concentrations after a single dose need not translate into measurably lower protection over that interval [30]. These are virological end points, whereas the DoRIS HPV 18 findings are serological. Lower HPV 18 antibody concentrations after a single dose have therefore not, within approximately five years of follow-up, translated into measurably reduced protection, but protective durability over 10–20 years remains uncertain. Because no immunological correlate of protection has been established, the antibody concentration required for long-term prevention of persistent HPV 18 infection is unknown. ESCUDDO enrolled HIV-negative girls in a setting with a different genotype distribution from most of Africa, so the inference should not be extended to PLHIV. Third, protection against non-vaccine types after a single dose remains incompletely characterized. Separately, in the DoRIS 9vHPV substudy, seropositivity after one dose was lower than that after two doses for three vaccine-included types—HPV 6, 45, and 52—although the clinical significance is uncertain because no correlate of protection has been established [23]. Reported delays in national decision making about single-dose adoption in high-HIV-burden countries reflect precisely these concerns [70]. Genotype-specific surveillance should therefore be incorporated into implementation where single-dose schedules are adopted at scale. Because the HPV 18 serological signal has been consistent across DoRIS analyses, HPV-18-specific infection outcomes should be reported separately within such surveillance.

7. HIV–HPV Co-Infection

7.1. Epidemiological Overlap

HIV and HPV burdens overlap geographically and demographically in SSA. Globally, an estimated 5.8% of cervical cancers are attributable to HIV, and WLHIV have approximately six times the risk of cervical cancer compared with women without HIV [39]. The concentration in Africa is stark: in SSA, 24.9% of cervical cancers are diagnosed in WLHIV and 20.4% are attributable to HIV, compared with 1.3% and 1.1%, respectively, in the rest of the world [38]. The HIV-attributable fraction is strongly age-dependent; in Southern Africa, it has been estimated at 86% in women aged 34 years or younger, falling to 12% in women aged 55 years and older, so that HIV-attributable disease is concentrated in younger women [38]. Consistent with this, record-linkage data from South Africa show WLHIV presenting with cervical cancer approximately a decade earlier than women without HIV [38].

7.2. Mechanisms of Increased Vulnerability

HIV-associated depletion and activation of cervical mucosal CD4 T cells may impair local immune control of HPV and contribute to HPV-associated cervical lesions [73]. Longitudinal meta-analyses indicate that HIV infection is associated with increased HPV acquisition and reduced HPV clearance; prevalent HPV infection has also been associated with increased HIV acquisition, supporting a bidirectional relationship [74]. Multiple-type infection is more common in PLHIV, increasing the probability that at least one persistent high-risk infection is present [19,20]. In the Harare cohort, HPV-related outcomes varied with markers of HIV disease and treatment history, although the observational design does not establish causality [36].

7.3. Genotype Distribution in People Living with HIV

Although HPV 16 remains important, PLHIV often have broader multiple-type distributions with a substantial non-16/18 high-risk HPV burden. In Harare, hrHPV prevalence among 2745 WLHIV attending routine screening was 53%, with HPV 58, 52, and 35 each as or more prevalent than HPV 16 [35]. In an earlier Harare cohort, 65% of hrHPV-positive WLHIV carried types other than HPV 16 or 18/45 [36]. At a rural Zimbabwean hospital, hrHPV was detected in 27% of HIV-positive versus 15% of HIV-negative women [17]. In Burundi, type distribution differed by HIV status and by urban or rural residence, and both HPV and HIV infection were independent risk factors for cervical lesions [19]. Ethiopian data indicate a higher HPV 35 contribution among HIV-positive than among HIV-negative women [52]. Table 3 summarizes HIV–HPV co-infection studies in SSA populations.

Three patterns emerge from Table 3. First, high-risk HPV prevalence among women living with HIV remains high even with long ART duration and viral suppression [35]. Second, in each SSA study that reported genotypes among women living with HIV or by HIV status, non-16/18 types, particularly HPV 35, 52, and 58, were prominent. Third, in the only longitudinal study, incident cervical disease occurred exclusively in hrHPV-positive women [36], supporting HPV-based screening in this population. The studies are cross-sectional or short-term, clinic-based, and mostly from Zimbabwe, so they describe disease burden rather than vaccine effect.

7.4. Role of Antiretroviral Therapy

Antiretroviral therapy (ART) modifies but does not abolish excess risk. A systematic review and meta-analysis found that ART use, and particularly sustained virological suppression and higher CD4 counts, was associated with reduced hrHPV prevalence and persistence and with reduced progression, and with increased regression, of cervical le-

sions in WLHIV; effects on invasive-cervical-cancer incidence were less clear [75]. In the Harare cohort, women on second-line ART were more likely to be hrHPV-positive, plausibly reflecting longer or less well-controlled disease history rather than a treatment effect [36]. Even among women with long ART duration and high rates of viral suppression, hrHPV prevalence remained 53% [35], and incident cervical disease in the earlier Harare cohort occurred only among hrHPV-positive women [36]. The operational conclusion is that ART expansion does not remove the need for cervical screening in WLHIV.

7.5. Vaccine Immunogenicity, Efficacy, and Post-Vaccination HPV Detection in People Living with HIV

Most vaccine evidence in PLHIV comes from three-dose immunogenicity studies. In a systematic review and meta-analysis of 18 independent studies, pooled seropositivity about 28 weeks after three doses was 99–100% for HPV 16 with all three vaccine types and 94–100% for HPV 18, but HPV 18 seropositivity 29–99 weeks after three doses of quadrivalent vaccine was 72% (95% CI 66–79), compared with 96% after bivalent vaccine and 94% in HIV-negative historical controls [11]. A later meta-analysis found lower HPV 16 and HPV 18 geometric mean titers in PLHIV than in people without HIV [12]. African data are consistent with this pattern. Among Kenyan children aged 9–14 years with perinatally acquired HIV who received three doses of quadrivalent vaccine, seroconversion at month 7 was 93.3–99.6% across vaccine types [76], but seropositivity at month 48 was 90% for HPV 16 and 77% for HPV 18, and persistence was lower in children with detectable viral load [77]. In South African women living with HIV aged 18–25 years, all recipients of three doses of bivalent vaccine remained seropositive for HPV 16 and HPV 18 at month 12 [78]. Evidence on reduced-dose schedules is limited to two doses: in a randomized trial among virologically suppressed women living with HIV in Belgium, two doses of nonavalent vaccine were non-inferior to three for seroconversion (97.7% versus 97.9%) [79]. Clinical efficacy data are sparse. In a Canadian cohort of girls and women living with HIV, the incidence of persistent quadrivalent-type infection after three doses was 2.3 per 100 person-years, lower than the 6.0 per 100 person-years reported in unvaccinated women living with HIV, and most breakthrough infections involved HPV 18 [80]. No correlate of protection has been established in PLHIV, and none of these studies evaluated a single dose.

Post-marketing data generated in SSA are still sparse but informative. In the ZIMGARD cohort at Newlands Clinic, Harare, 98 adolescents and young adults with perinatally acquired HIV were assessed a mean of six years after quadrivalent vaccination. Any HPV was detected in 68/98 participants (69%): 38/98 (39%) had both high- and low-risk types, 17/98 (17%) had high-risk types only, and 13/98 (13%) had low-risk types only. The authors proposed possible waning of HPV 18 immunity and reduced cross-protection against HPV 45 as hypotheses [37]. However, the cross-sectional study lacked prevaccination measurements and an unvaccinated comparator and therefore cannot establish waning immunity, infection timing, or vaccine effectiveness. A separate UK cohort of people with perinatally acquired HIV found no vaccine-type HPV 16/18 among vaccinated participants but lower HPV 18 than HPV 16 seropositivity, with the two HPV-16/18-seronegative vaccinated participants both having detectable viremia and CD4 counts below 200 cells/mm3 [81]. A prospective Rwandan cohort has been established specifically to measure long-term HPV vaccination effectiveness and immunity in women living with and without HIV [82].

7.6. Implications for Vaccination Schedules in People Living with HIV

WHO continues to recommend two or three doses for immunocompromised individuals, including PLHIV, rather than a single dose [5]. That position is consistent with the current evidence: we identified no published randomized trial of single-dose efficacy in PL-

HIV, DoRIS enrolled only HIV-negative girls, and KEN SHE was not designed to answer this question [21,26]. Observational data are beginning to emerge: in a South African district where single-dose bivalent vaccine was delivered through a school-based campaign, HPV 16/18 prevalence among girls living with HIV was 37% lower after vaccination (adjusted prevalence ratio 0.63, 95% CI 0.41–0.95) in repeat cross-sectional surveys [56]. This design cannot establish individual-level efficacy or durability, but it shows that population-level effects are measurable in a high-HIV-burden setting. Randomized evidence is in progress: HOPE-II is evaluating single-dose nonavalent vaccination in previously vaccinated women living with HIV in South Africa, Botswana, and Rwanda (NCT06436274), and OPTIMO is comparing one, two, and three doses in children and adolescents living with HIV in Peru, Brazil, and Haiti [83]. Given lower antibody titers reported in PLHIV, uncertainty regarding the durability of HPV 18 responses, and the broader genotype distribution in this population, extrapolating single-dose findings to PLHIV is not currently justified. Two implications follow for programs in SSA: countries adopting single-dose schedules for the general adolescent population need an explicit, funded pathway to deliver a multidose schedule to adolescents living with HIV, which in practice requires linkage between HIV services and immunization programs. Such linkage appears feasible. HPV vaccination has been offered within HIV care at Newlands Clinic in Harare since 2015 [36]; an implementation study that integrated HPV vaccination into HIV services in 54 facilities in Mozambique and Zimbabwe reported two-dose completion in 49.1% and 73.9% of eligible girls, respectively [84]; and a quality-improvement project in two Ugandan HIV care centers reported 92% completion [85]. However, a policy review in Eswatini, Malawi, and Uganda found that none had fully documented or consistently implemented strategies to deliver additional doses to immunocompromised girls [86], and we identified no published estimate of the cost of such a pathway. This element of the recommendation therefore still requires costing and implementation evaluation. Dedicated immunogenicity, immunobridging, durability, and effectiveness studies in PLHIV are a priority [5,52].

8. Discussion

Cervical-cancer prevention in SSA is constrained less by the absence of an effective vaccine than by the terms on which that vaccine is delivered. The three bodies of literature examined in this review bear on those terms in different ways, and the evidence they contain is best read together. Reduced-dose vaccination, the intervention most likely to raise coverage quickly across the region, is now supported by randomized evidence in immunocompetent adolescents. The products through which coverage is currently delivered do not cover every high-risk genotype commonly reported in African populations. The group carrying a disproportionate share of HPV-attributable disease in the region is the one for which single-dose protection has not been established by the evidence reviewed here. These findings inform three separate program decisions: how to expand vaccination coverage, which HPV genotypes are directly targeted by the vaccine product, and which dose schedule is appropriate for PLHIV. Evidence supporting a single-dose schedule in immunocompetent populations does not, by itself, determine the most appropriate vaccine product or establish that one dose provides sufficient protection for PLHIV.

The case for dose reduction has moved from inference to direct demonstration over approximately five years. Post-hoc analyses of the Costa Rica Vaccine Trial and the IARC India cohort first indicated that one dose conferred protection comparable to that of multidose schedules, with antibody stability in the former subsequently documented for up to 16 years [31–33]. Randomized efficacy data from KEN SHE initially showed efficacy exceeding 97% against persistent HPV 16/18 infection at 36 months. At 54 months, single-dose vaccine efficacy was 99.3% (95% CI 96.2–99.9) against incident persistent HPV 16/18

infection and 98.9% (95% CI 94.9–99.8) against persistent infection with the seven high-risk types included in the nonavalent vaccine [28]. ESCUDDO has since supplied the head-to-head randomized comparison that this literature previously lacked, finding one dose non-inferior to two doses against persistent HPV 16/18 infection for both the bivalent and the nonavalent vaccine [30]. Two qualifications warrant emphasis. No immunological correlate of protection has been established for HPV vaccines, so non-inferior antibody concentrations support but cannot establish equivalent efficacy [24,25,66]. Furthermore, HPV 18 antibody responses after a single dose have repeatedly failed prespecified non-inferiority criteria even where seropositivity remained high, although the five-year efficacy findings in ESCUDDO suggest that this serological difference need not translate into measurably reduced protection over that interval [21,22,30]. In settings where coverage is the principal constraint, modeling and costing analyses indicate that reallocating doses to extend vaccine reach may avert more cervical cancer than maintaining a two-dose schedule in a supply- and financing-constrained environment [67–69].

The genotype literature points in a different direction, and the two should not be conflated. Non-16/18 high-risk types account for a substantial share of infections reported in African study populations, with HPV 35, 52, 45, 33, and 58 recurring across subregions [8,9,17,35]. HPV 35 merits particular attention: it is prominent in African cancer specimens, is not included in any licensed vaccine, and shows sublineage-level associations with precancer in women of African ancestry, although these associations do not establish greater oncogenic potential [7]. Coverage-gap analyses from Zimbabwe and Ethiopia estimate that a substantial minority of circulating high-risk types would remain uncovered even by the nonavalent vaccine [6,52]. Such estimates describe genotype coverage rather than vaccine effectiveness, and the qualifications set out in Section 5.3 apply: oncogenic potential differs markedly between types, partial cross-protection has been documented for some non-vaccine types, and most estimates derive from screening rather than cancer specimens. Where cancer specimens have been genotyped, the non-16/18 contribution is concentrated in HPV 35 and HPV 45 [9,51]. The direction of the evidence is nonetheless consistent, and it suggests that dosing and valency address largely different problems, although they are not independent. Dose reduction primarily determines how many girls are reached, and valency, together with continued screening, primarily determines what those girls are protected against. However, 36 months after a single dose of the nonavalent vaccine, seropositivity for HPV 45 and HPV 52 was lower than that after two doses (73.0–87.7% versus 98.6%) [23], so the number of doses may also influence the breadth of the antibody response to the additional nonavalent types. Whether this matters clinically is not yet known: single-dose nonavalent efficacy against the seven oncogenic vaccine types combined was 98.9% at 54 months in KEN SHE [28], but that pooled end point was not designed to assess HPV 45 and HPV 52 individually, and no correlate of protection has been established.

HIV modifies every strand of this literature. It is associated with higher HPV acquisition and reduced clearance, shifts genotype distribution further toward non-vaccine types, attenuates vaccine antibody responses, and moves cervical cancer to younger ages [12,38,74]. In SSA, approximately one in five cervical cancers is attributable to HIV, and, in Southern Africa, the attributable fraction among women aged 34 years or younger has been estimated at 86% [38,39]. In the countries carrying the highest cervical-cancer burden, this is not a small subgroup. It is also the one population for which no published randomized single-dose evidence was identified: DoRIS enrolled HIV-negative girls, KEN SHE was not designed to address the question, and ESCUDDO was conducted in an immunocompetent population in a setting with a different genotype distribution [21,26,30]. WHO continues to recommend two or three doses for immunocompromised individuals, and the evidence

reviewed here supports retaining that distinction rather than extrapolating across it [5]. Cross-sectional post-marketing observations concerning HPV 18 immunity among adolescents with perinatally acquired HIV, although hypothesis-generating, illustrate the need for longitudinal post-introduction surveillance [37,81]. On this reading, the reported hesitancy of immunization stakeholders in high-HIV-burden countries about adopting single-dose schedules reflects a genuine evidence gap rather than an obstacle to be overcome [70].

Two categories of limitation apply. The first concerns the literature reviewed. Prevalence and genotype estimates are drawn from studies that differ in population, specimen type, assay type coverage, and analytical sensitivity, so cross-study comparison is approximate; the tables presented here report those characteristics alongside the estimates for that reason. Much of the African genotype data derives from screening or clinic populations rather than from cancer specimens, which makes inference about oncogenic contribution indirect. The geographical coverage of the evidence was uneven: studies from Eastern and Southern Africa, particularly Kenya, Tanzania, South Africa, and Zimbabwe, were more prominent than evidence from Western and Central Africa. The findings should therefore not be interpreted as uniformly representative of all SSA countries or subregions. This unevenness affects the review's conclusions differently. The single-dose efficacy and immunogenicity findings concern vaccine performance in immunocompetent recipients and have been replicated in Tanzania, Kenya, Costa Rica, and India [21,27,30,33], so they depend less on regional epidemiology. The genotype conclusions are more location-dependent: the largest multicountry study of invasive cancer specimens from the region, which included cases from Ghana and Nigeria, identified HPV 16, 18, 45, and 35 as the most common types [9], but data from Central Africa remain particularly sparse [8]. The HIV-related conclusions apply most directly to Southern and Eastern Africa, where the HIV-attributable fraction of cervical cancer is highest [38]. Expanded genotype surveillance in Western and Central Africa is therefore a priority. Post-vaccination genotype surveillance in African populations remains limited, so type replacement and cross-protection cannot yet be assessed empirically in the settings where they matter most. The second concerns this review. It is narrative rather than systematic; sources were selected for relevance to three predefined objectives rather than by formal eligibility criteria; and no risk-of-bias appraisal or quantitative synthesis was undertaken. Selection bias therefore cannot be excluded, although the risk was reduced by retaining evidence that qualified the conclusions and by checking those conclusions against independent systematic reviews, and the account given here should be read as an interpretation of a heterogeneous literature rather than as a pooled estimate of any parameter.

9. Conclusions

The evidence reviewed here bears on three distinct decisions rather than one. For immunocompetent adolescents, the evidence supports single-dose implementation, provided that it is accompanied by long-term monitoring of protection; the main remaining uncertainty is durability over the decades relevant to cancer prevention, which continued follow-up of existing trial cohorts can resolve. For people living with HIV, the evidence does not yet support dose reduction, and the more immediate gap is operational: few countries have documented how adolescents living with HIV will be identified and offered additional doses once general schedules change. For product choice, regional genotype data argue for cancer-weighted, country-specific comparison of vaccines, particularly where HPV 35 and HPV 45 are prominent in cancer specimens, but they do not, by themselves, justify a change of product. In all three cases, cervical screening remains necessary for vaccinated and unvaccinated cohorts alike.

For policy, countries adopting single-dose schedules should couple implementation with a costed and funded pathway, building on existing HIV-service-delivery models, for multidose vaccination of adolescents living with HIV and with sentinel genotype-specific post-introduction surveillance. Vaccine procurement and Gavi-support decisions should consider country-specific, cancer-weighted genotype distributions when comparing bivalent, quadrivalent, and nonavalent products. Screening programs should assume that vaccinated cohorts will retain residual risk from non-vaccine types, with screening for WLHIV integrated into HIV care.

Much of the evidence that has informed global HPV dose-reduction policy was generated through trials in Tanzania and Kenya involving investigators and institutions in SSA. The remaining priorities include establishing single-dose adequacy in PLHIV, clarifying the carcinogenic contribution of regionally prevalent genotypes, and strengthening post-vaccination surveillance. Sustained investment in research capacity and collaboration with global partners will be important components of cervical-cancer elimination efforts in SSA.

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Abbreviations

The following abbreviations are used in this manuscript:

ART	antiretroviral therapy
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CVT	Costa Rica Vaccine Trial
DoRIS	Dose Reduction Immunobridging and Safety Study
GMC	geometric mean concentration
HIV	human immunodeficiency virus
HPV	human papillomavirus
hrHPV	high-risk human papillomavirus
HR	high-risk
IARC	International Agency for Research on Cancer
KEN SHE	Kenya Single-dose HPV-vaccine Efficacy study
LMIC	low- and middle-income country
LR	low-risk
PLHIV	people living with HIV
SSA	sub-Saharan Africa
STI	sexually transmitted infection
VLP	virus-like particle
WHO	World Health Organization
WLHIV	women living with HIV
2vHPV	bivalent HPV vaccine
4vHPV	quadrivalent HPV vaccine
9vHPV	nonavalent HPV vaccine

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