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Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa

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ABSTRACT

Background: Women in sub-Saharan Africa have high dual burden of HPV and HIV infections, which can interact to increase cervical cancer (CC) risk. The 9-valent HPV (9vHPV) vaccine has high demonstrated effectiveness against HPV types causing 90% of CC. Additionally, one dose of the 9vHPV vaccine has the potential to achieve greater coverage at lower costs than a two-dose schedule. However, the potential impact of single-dose 9vHPV vaccine accounting for HPV-HIV interactions has not been estimated.
Methods: We adapted a dynamic HIV transmission model to include HPV acquisition and CC pathogenesis and projected the impact of a single dose 9vHPV preadolescent vaccination in KwaZulu-Natal, South Africa. We report health impacts of HPV vaccination separately for HIV-positive women stratified by HIV treatment and CD4 count and HIV-negative women.
Results: At 90% coverage of females age 9 years with 80% lifelong vaccine efficacy, single dose HPV vaccination was projected to reduce CC incidence by 74% and mortality by 71% in the general female population at 70 years after the start of the vaccination program. Age-standardized CC incidence and mortality reductions were comparable among HIV-negative women, HIV-positive women, and HIV-positive women on ART. Health benefits were reduced when assuming waning protection at 10, 15 and 20 years after vaccination.
Discussion: Single dose 9vHPV vaccination is projected to avert substantial CC burden in South Africa and similar high HIV prevalence settings. Health benefits were comparable across all female subpopulations stratified by HIV status, CD4 count, and ART status.

1. Introduction

Cervical cancer (CC) is the most common cause of cancer among women in sub-Saharan Africa (SSA), with an estimated 93,000 cases occurring annually [1]. CC rates in SSA are the highest in the world and age-standardized CC mortality rates are 19.9 per 100,000 person-years, 7-times higher than those of developed regions [1], In the absence of prevention, CC rates in SSA are projected to increase over the next 20 years due to lack of organized screening programs and the high burden of HIV infection [2]. Infection with HIV is associated with increased HPV acquisition [3,4], decreased HPV clearance, lower regression of precancerous cervical lesions [3,5], increased lesion progression [6,7], and higher CC incidence [8]. The interaction between HIV and HPV has been shown to be modified by CD4 count, with higher persistence and progression of HPV-associated disease with decreasing CD4 counts. Compared to HIV-negative women, HIV-positive women with CD4 count $\geq$350 have been shown to have 1.7-times the risk of CC while HIV-positive women with CD4 < 200 have a dramatically higher CC risk (8.4-times) [9].

As the life expectancy of HIV-positive women increases with the expanding availability of antiretroviral therapy (ART), the number of CC cases is projected to increase [10]. While ART has decreased the incidence of other AIDS-related cancers, its relation-

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ship with CC is unclear, with some studies finding no change in CC incidence while others find a reduction in precancerous lesions and CC [11,12]. Countries in SSA have a high dual burden of HPV and HIV. In particular, South Africa has the highest HIV burden in the world: 5.7 million people currently infected, 60% of whom are women. Estimates show that 54% of HIV-positive women in South Africa are co-infected with high-risk HPV compared to 18% of HIV-negative women [13]. CC screening coverage is low and opportunistic in SSA, and HIV-positive women who are unaware of their status or have not yet accessed ART are even less likely to undergo screening. In South Africa, less than 20% of women have been screened for CC [14], and screening scale-up is hindered by the shortage of healthcare professionals, infrastructure, and essential medical equipment [15].

HPV vaccination offers promising primary prevention for CC, particularly in the absence of widespread screening. Both the bivalent and quadrivalent vaccine, which provide protection against HPV types 16 and 18 (responsible for 70% of CC), have shown close to 100% efficacy against persistent HPV infection in both HIV-negative and positive women [16–18]. The recently approved 9-valent (9vHPV) vaccine provides almost 100% protection against 5 additional high-risk HPV types (HPV-31, 33, 45, 52, and 58) while generating an antibody response to HPV-16, 18 that is non-inferior to the quadrivalent HPV vaccine, protecting against an estimated 90% of CC [19]. Since HIV-positive women, have higher prevalence of abnormal cytology [20] and greater prevalence of non-HPV 16 and 18 in precancerous lesions than HIV-negative women [21], implementing 9vHPV vaccine in countries with high HIV burden can reduce screen detected lesions. This is particularly relevant data on cross-protection for HPV-16/18 vaccines is limited, particularly for fewer than 3 vaccine doses.

Although HPV vaccines were originally evaluated in a three-dose schedule, recent evidence shows that two doses can offer equivalent protection and many countries have moved to implementing two doses of HPV vaccine [22]. Further, emerging evidence shows one dose of HPV vaccine can protect against persistent HPV infection (96% efficacy) although data on efficacy and duration of one-dose protection are limited and studies were not designed to evaluate one-dose schedules [22,23]. A single dose vaccine has the potential to achieve higher coverage than a two-dose schedule at lower costs. This is especially important for many SSA countries where the HIV burden is high but where the high cost of HPV vaccine programmes has to date proved a deterrent to introduction. In 2014, the South Africa National Department of Health began a 2-dose school-based campaign of bivalent HPV vaccination for girls age 9 years and older in grade 4. Close to 16,500 schools were visited by the campaign and coverage for one dose vaccine was 93% [15]. In this analysis, our objective was to evaluate the impact of the single-dose 9vHPV vaccine in a high HIV prevalence setting while accounting for the interaction between HIV and HPV. We simulated single dose 9vHPV vaccination in KwaZulu-Natal, South Africa—a region with high HIV prevalence (28%) [24]. The simulation accounts for the HIV epidemic and evaluates the health benefits of HPV vaccination stratified by HIV and ART status. Results can assist policy makers in SSA in making decisions about HPV vaccine introduction and in developing HPV vaccination guidelines.

2. Methods

2.1. Mathematical model

We adapted a previously developed dynamic compartmental model of HIV infection in KwaZulu-Natal, South Africa to include HPV infection and cervical cancer pathogenesis (Fig. 1) [25,26]. The model incorporates herd protection and can evaluate the

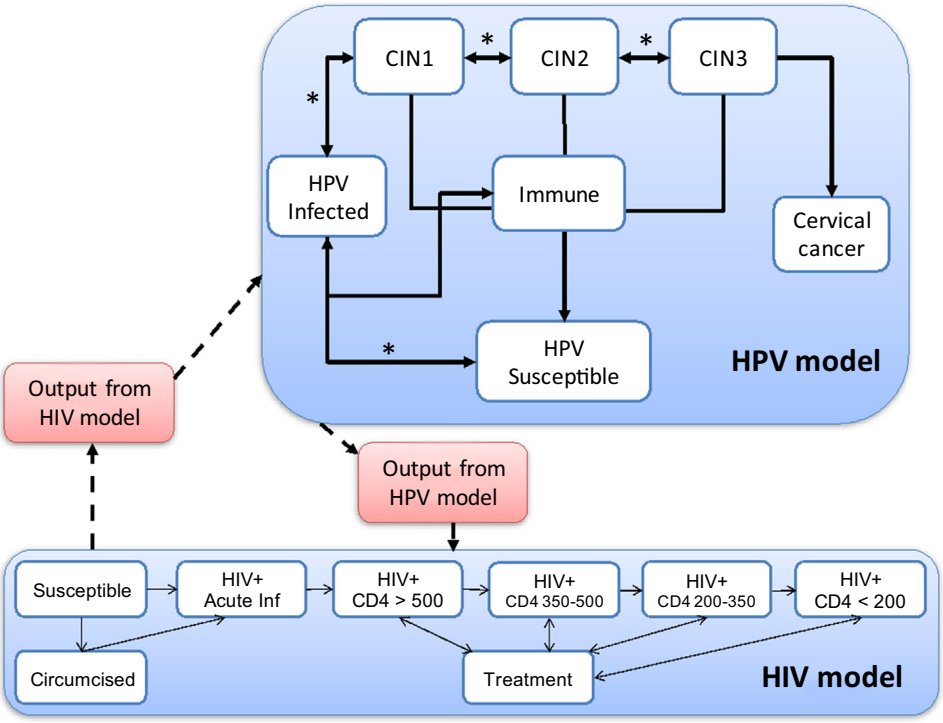

Fig. 1. Simplified model schematic. While HIV and HPV state progression occurs simultaneously in the model, here it is depicted separately for simplicity. The population flows through the HPV model and can acquire HPV through sexual mixing. Females can then transition to precancerous lesions and CC. HPV vaccination (not shown) reduces risk of HPV acquisition. The population then flows through the HIV model where susceptible persons can acquire HIV and progress through CD4 disease stages. Transitions with * indicate that HPV-related progression and regression depends on HIV status and CD4 count. Background mortality and excess mortality due to HIV and CC are not shown.

impact of HPV vaccination strategies under varying HIV epidemics stages and HIV prevalence.

2.2. HIV infection

In brief, the HIV model, validated for HIV transmission in KwaZulu-Natal, South Africa, simulates the natural history of HIV/AIDS [25]. Men and women are stratified by age group, sexual activity, viral load, and CD4 count. Susceptible individuals can acquire HIV and transition to acute infection. The force of HIV infection is estimated as a function of sexual mixing (by age and sexual activity), proportion of HIV infected individuals of the opposite sex, circumcision, and HIV transmission probability dependent on viral load. For HIV-positive persons, CD4 count and viral load changes over time are based on clinical estimates from a prospective cohort.

2.3. HPV infection

We added HPV infection to the existing HIV model. Susceptible females can acquire high-risk (HR) HPV infection from a male sexual partner and develop precancerous lesions categorized as cervical intraepithelial neoplasia, grades 1, 2, or 3 (CIN 1, 2, or 3). HPV infection and CIN123 lesions can regress to normal over time and females with CIN 3 can develop cervical cancer (categorized in 3 stages: local, regional, and distant). We assume females who clear their HPV infection can develop low-level natural immunity (1–10% protection against subsequent infections of the same type) while males who clear HPV infection do not develop natural immunity. The model estimates the force of HPV infection as a function of sexual mixing (by age and sexual activity), proportion of HPV infected individuals of the opposite sex, and HPV transmission probability dependent HIV status and CD4 count if HIV-positive. Once females are infected, the probability of HPV disease progression is governed by age, HIV-status, and CD4 count if infected with HIV. HIV-positive females have a higher risk of HPV acquisition and CIN1-2 progression and a lower probability of disease regression and infection clearance. HPV disease progression is inversely related to CD4 count; women at the lowest category CD4 counts are least likely to clear and more likely to experience disease progression.

2.4. Model parameters and calibration

The HIV natural history and sexual behavior parameters are based on a recent, validated HIV transmission model for KwaZulu-Natal, South Africa [25]. Model parameters were initially established using the best available information on the natural history of HIV and HPV infection, ART uptake, sexual behavior, cervical carcinogenesis, and HPV/HIV interaction (Supplemental Appendix). The model was then calibrated to fit the setting of KwaZulu-Natal, South Africa using a maximum likelihood-based approach that allowed parameters to vary over plausible ranges. Changes in the population over time were estimated using a system of ordinary differential equations (ODEs) that were solved in MATLAB version 2017 using 4th-order Runge-Kutta methods [27]. Additional details about the model, data sources, parameters, and calibration results are available in the Supplemental Appendix.

2.5. Vaccination strategies

We modeled the impact of one-dose 9vHPV vaccine for girls age 9 years assuming 80% lifelong effectiveness and protection against 90% of CC with no cross protection for non-vaccine HPV types. Vaccine coverage was assumed to be 90%. We evaluated the impact of a vaccination program starting in 2018 over a 70 year time horizon to capture the lifetime cancer risks of the first cohorts of vaccinated girls.

2.6. Sensitivity analyses

We varied vaccine coverage from 50 to 90% of 9 year-old girls. Due to the uncertainty in the carcinogenic evolution of HPV precancers to cervical cancer, the same analysis was performed under scenarios wherein the CIN3 to CC progression rate was varied from 0.5 times to 1.5 times the base value. Duration of vaccine protection was varied from lifelong (base case) to 10, 15, and 20 years, after which we assumed a 20-year linear decline in efficacy until the vaccine reached zero protection. Finally, a scenario with full vaccine efficacy and life-long protection was evaluated.

3. Results

3.1. Model calibration

A HIV model that was previously validated for KwaZulu-Natal, South Africa was adapted in the current study. The model displayed good fit to primary data for age-specific HIV prevalence, HPV prevalence, CIN 2–3 prevalence, and CC incidence, as well as HIV prevalence and ART coverage over time from South Africa (Fig. 2 and Supplemental Appendix). We assumed ART-scale and viral suppression with 60% coverage of HIV-positive individuals, just short of the UNAIDS goal of 73% of HIV positive persons suppressed required to achieve HIV epidemic control. This reduced HIV prevalence to 5% by year 70 (2077) of the vaccination program.

3.2. Health effects of 9vHPV vaccination

Assuming 90% coverage of females age 9 years and 80% lifelong vaccine efficacy, 9vHPV was projected to reduce CC incidence by 74% at year 70 after the start of a vaccination program (Fig. 3A, Table 1). Vaccinating girls at lower coverage rates of 50% and 70% was projected to avert 62% and 48% of CC at year 70, respectively (Table 1). Across all scenarios, the relative reduction in age-standardized CC incidence was comparable across all CD4 count levels. Assuming 90% vaccine coverage and waning starting at 20 years was associated with 2% lower reductions in CC incidence for the full female population. Health benefits declined with faster

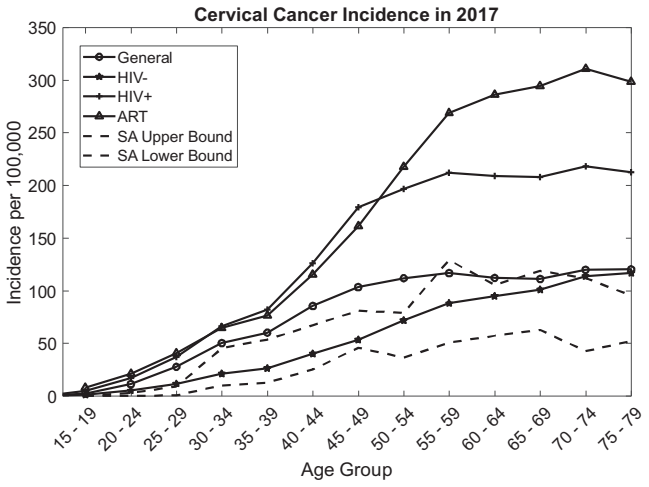

Fig. 2. Model-estimated CC incidence in 2017 compared to empirical data from 2012 Globocan (green line) and CC registries in South Africa (black dotted line). Upper bound and lower bound refer to the 95% bounds of the South African cancer registry data.

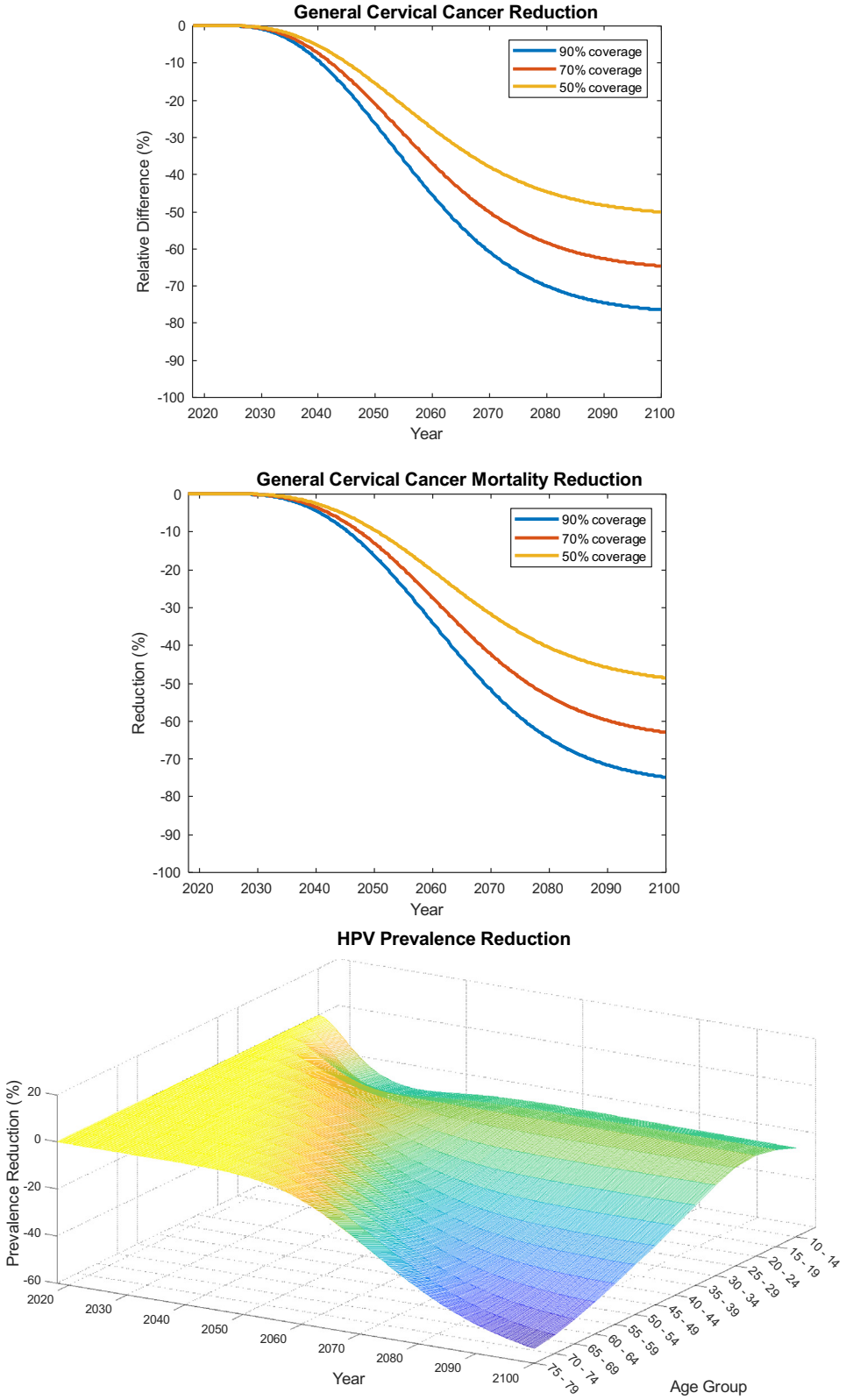

Fig. 3. Estimated population-level impact of single-dose 9vHPV vaccination of preadolescent girls in KwaZulu Natal, South Africa. Estimated percentage change in CC incidence (A), CC mortality (B), and age-specific HPV prevalence (C) following vaccination the start of a vaccination program (year 2017) over the first 70 years of the program. Base-case assumptions: Vaccine effectiveness: 80%, duration of vaccine protection: Lifelong.

time to waning, with 2% and 7% lower CC incidence reduction (compared to lifelong vaccine protection) for waning at 15 and 10 years respectively.

Table 2 and Fig. 2B display the impact of 9vHPV vaccination on CC deaths under varying scenarios of vaccine coverage and waning. At 90% coverage, HPV vaccination was projected to avert 71% of CC

Table 1
Percent reduction (%) in age-standardized CC incidence 70 years after start of preadolescent 9vHPV vaccination program in KwaZulu-Natal, South Africa with varying vaccine coverage and waning.[a]

	Total female population	HIV-negative females	HIV-positive females on ART	HIV-positive females with CD4 > 500	HIV-positive females with CD4 350–500	HIV-positive females with CD4 200–350	HIV-positive females with CD4 < 200
Lifelong vaccine protection (varying coverage)							
50%	48	49	48	49	49	50	49
70%	62	64	62	64	64	65	64
90%	74	76	73	76	76	77	77
Vaccine waning (90% coverage)							
20 years	72	74	72	74	74	75	75
15 years	71	72	71	72	73	73	74
10 years	67	67	67	67	68	70	70

[a] Shown are the percent reductions in cervical cancer (CC) incidence compared to status quo (no HPV vaccination or CC screening and background ART scale-up) associated with HPV vaccination at 80% efficacy for: the full population of females, HIV-negative females, and HIV-positive females stratified by ART status and CD4 count (if not on ART). For vaccine strategies with waning, HPV vaccine effectiveness was assumed to linearly decline over 20 years start at 10, 15, and 20 years post-administration.

Table 2
Percent reduction (%) in CC mortality 70 years after start of preadolescent 9vHPV vaccination program in KwaZulu-Natal, South Africa with varying vaccine coverage and waning.[a]

	Total female population	HIV-negative females	HIV-positive females on ART	HIV-positive females with CD4 > 500	HIV-positive females with CD4 350–500	HIV-positive females with CD4 200–350	HIV-positive females with CD4 < 200
Lifelong vaccine protection (varying coverage)							
50%	45	47	43	48	48	48	48
70%	59	62	56	62	62	62	62
90%	71	73	67	74	74	74	74
Vaccine waning (90% coverage)							
20 years	69	72	68	72	72	74	74
15 years	68	70	67	70	72	72	72
10 years	63	65	63	65	66	67	68

[a] Shown are the percent reductions in cervical cancer (CC) mortality compared to status quo (no HPV vaccination or CC screening and background ART scale-up) associated with HPV vaccination at 80% efficacy for: the full population of females, HIV-negative females, and HIV-positive females stratified by ART status and CD4 count (if not on ART). For vaccine strategies with waning, HPV vaccine effectiveness was assumed to linearly decline over 20 years start at 10, 15, and 20 years post-administration.

deaths at year 70 in the general female population. At 50% and 70% vaccine coverage, reductions in CC mortality in the general population were lower (45% and 59% respectively). Vaccine waning at 90% coverage had lower mortality reductions, 69%, 68%, and 63% with waning beginning at 20, 15, and 10 years, respectively, after vaccine administration. Similar to CC incidence, relative reductions in age-standardized mortality were comparable across CD4 counts, ART status, and HIV status. When a single-dose of the vaccine was assumed to confer complete protection with life-long efficacy, HPV vaccination was projected to avert 82% of incident CC and 79% of CC mortality in the general population 70 years after the start of the vaccination campaign.

Varying the CIN3 to CC progression rate from 0.5 times to 1.5 times the base value had a marginal impact on the estimated CC incidence and mortality reductions. Under the 90% coverage scenario, reductions in CC incidence ranged from 73% to 74% while reductions in CC mortality ranged from 69% to 71% in the general female population.

Reductions in HPV prevalence due to vaccination appeared earliest in the younger age groups. Over time, these reductions also appeared in the older age groups as vaccinated individuals aged into them and gradually constituted a larger proportion of the population. These reductions in HPV prevalence were followed by a concomitant decrease in CC incidence and mortality. When assuming 80% vaccine efficacy and multiple waning scenarios, comparable reductions were observed in all female populations 70 years after the start of the simulated vaccination program. The magnitude of these reductions at year 70 remained relatively stable when varying the progression rate of CIN3 to CC from 0.5 times to 1.5 times the base value. Given that all cervical cancers originate from an incident oncogenic HPV infection, it may be inferred that primary prevention of the incident infection will lead to comparable long-term reductions in mortality and CC incidence over a range of plausible CIN3 to CC natural history scenarios (see Table 3).

4. Discussion

In this dynamic transmission modeling analysis of HIV/HPV co-infection, we project that single dose 9vHPV vaccination at 90% coverage of preadolescent girls has the potential to avert over 95% of HPV incidence and 70% of CC incidence and mortality in KwaZulu-Natal, South Africa, which may be generalizable to similar settings. Relative reductions in CC incidence and mortality were comparable across female subpopulations stratified by CD4 count, HIV status, and ART status.

Table 3
Percent reduction (%) in HPV Incidence 70 years after start of preadolescent 9vHPV vaccination program in KwaZulu-Natal, South Africa at 90% vaccination coverage with lifelong protection.

Lifelong vaccine protection (varying coverage)	Total female population	HIV-negative females	HIV-positive females	HIV-positive females on ART
50%	74	77	76	69
70%	86	88	87	83
90%	95	96	96	94

Our conclusions are dependent on 9vHPV vaccine coverage, efficacy, and duration of protection. The potential for 90% vaccine coverage has been observed in a large-scale school-based demonstration project in South Africa that achieved over 90% coverage of single-dose HPV vaccine among preadolescent girls in grade 4 [15]. However, even at lower coverage of 50 and 70% of preadolescent girls, 9vHPV is projected to have a considerable impact on CC burden. Further, the efficacy and duration of single dose 9vHPV are currently not known, although they are likely to be similar to the bivalent and quadrivalent vaccines. Previous studies of the bivalent and quadrivalent vaccine show close to 100% efficacy of one dose against persistent HPV infection at 4–6 years after vaccine administration [22,23]. However, currently no data are available on duration of vaccine protection after 6 years and it is uncertain how results from bivalent and quadrivalent vaccine duration will translate to 9vHPV projection. Therefore we evaluated several plausible scenarios of vaccine waning. While waning at 20 years is associated with small reductions in CC incidence and mortality reductions, health benefits decline with waning at 15 and 10 years, likely due to the timing of peak age of CC incidence.

Our results are subject to certain limitations. We modeled oncogenic HPV types in three categories (HPV 16/18, other 9v vaccine types, and non-vaccine types), so we could not account for differences in HPV progressions by specific types. Further, we did not assess reductions in precancerous lesions. While HIV-positive women have similar HPV type distribution in CC as HIV-negative women, they have a high incidence of precancerous cervical lesions and a greater diversity of HPV types in their lesions which infrequently progress to CC [28]. Therefore, 9vHPV vaccination has the potential to achieve significant reductions in precancerous lesions in HIV-positive women and increase the efficiency of CC screenings by reducing costs associated with overdiagnosis and overtreatment. Further, our study did not include costs associated with HPV vaccination or treatment of lesions and cancer. Cost-effectiveness of 9vHPV vaccination will be an important driver in the decision to implement the vaccine, particularly in low-and-middle-income country (LMIC) settings. While the cost of 9vHPV for South Africa and similar settings is not yet available, future modeling studies should identify a threshold for the vaccine's cost at which 9vHPV would be cost-effective in SSA. Also, there are uncertainties in the natural history of HPV, the interaction between HPV and HIV, and single-dose HPV vaccine effectiveness and duration of protection. We calibrated the model across plausible ranges and performed sensitivity analyses to reflect the impact of uncertainty regarding parameters for CIN3 progression to CC and duration of HPV vaccine protection. Finally, there are uncertainties about HPV vaccine efficacy once a woman acquires an HIV infection. As more epidemiologic data become available, this analysis should be revisited. Our analysis shows that even with high waning, HPV vaccination can be effective in reducing CC morbidity and mortality. Future analyses should examine scenarios of reduced HPV vaccine efficacy after HIV acquisition.

Our analysis has several strengths. We utilized a comprehensive model of HIV/HPV natural history to assess the health impact of 9vHPV vaccine on women stratified by HIV infection, CD4 count, and ART status. We account for the effect of the HIV epidemic on HPV infection, precancerous lesions, and CC cancer over time as the proportion of individuals on ART is projected to increase. We explicitly capture age at vaccination, and acquisition of HIV and HPV. We show that in high HIV burden settings, despite the increased risk for HPV acquisition among HIV-positive women, the single-dose 9vHPV vaccination has the potential to avert substantial CC burden. The directionality of our results are likely generalizable to one dose HPV16/18 vaccination strategies as the impact of HIV on HPV incidence is similar by type. These results can be useful to policymakers in SSA as they choose interventions to avert this leading causes of mortality.

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Conflict of interest

The authors have no conflicts to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.023.

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