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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

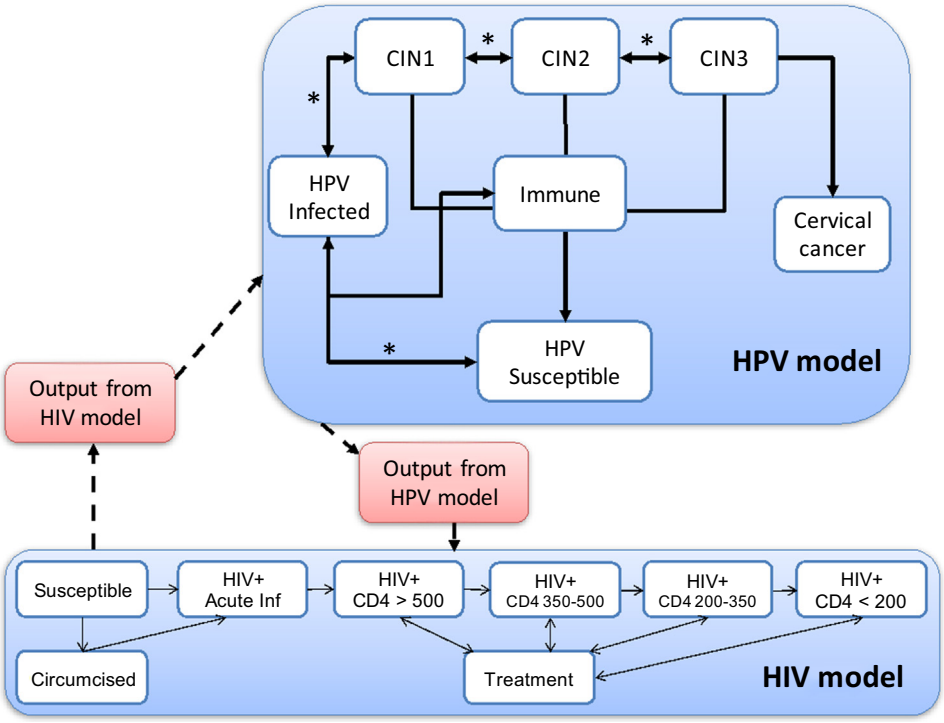

Fig. 1. Simplified model schematic. While HIV and HPV state progression occurs simultaneously in the model, here it is depicted separately for simplicity. The population flows through the HPV model and can acquire HPV through sexual mixing. Females can then transition to precancerous lesions and CC. 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.

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