2011

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Original Publication Citation

Tracy, L., Gaff, H. D., Burgess, C., Sow, S., Gravitt, P. E., & Tracy, J. K. (2011). Estimating the impact of Human Papillomavirus (HPV) vaccination on HPV prevalence and cervical cancer incidence in Mali. *Clinical Infectious Diseases, 52*(5), 641-645. doi:10.1093/cid/ciq190

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Estimating the Impact of Human Papillomavirus (HPV) Vaccination on HPV Prevalence and Cervical Cancer Incidence in Mali

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Human papillomavirus vaccines have potential to reduce cervical cancer incidence and mortality; however, cultural and economic barriers may hinder success in developing countries. We assessed impact of a single vaccine campaign in Mali with use of mathematical modeling. Our model shows that decreases in the prevalence of Human papillomavirus infection are proportional to achieved vaccination coverage.

Persistent infection with certain viral strains of human papillomavirus (HPV) is a necessary cause of cervical cancer [1]. Licensed vaccines to prevent cervical cancer represent a significant public health breakthrough that may benefit women worldwide; however, this will only be realized if vaccines are delivered to populations in greatest need. Developing countries bear the greatest cervical cancer burden, with ~80% of cervical cancer–associated deaths [2] but are least likely to benefit from HPV vaccines owing to limited resources necessary for acquiring and delivering the 3-dose regimen. In addition, vaccinating women before sexual debut is especially challenging in sub-Saharan Africa [3] because of limited health care funding, rare reproductive health services, and dispersed populations. Some estimates suggest that HPV vaccines will be feasible in countries with low socioeconomic status (ie, gross domestic product <US$1000 per capita) only if the per-dose cost is reduced to US$1–2 [4].

Mali is a landlocked sub-Saharan West African country with an estimated 12.3 million persons [5, 6]. Cervical cancer is the most common cancer among Malian women, with an annual age-adjusted incidence rate of 35.2 cases per 100,000 population [2]; it is also the leading cause of cancer-related mortality. Because of economic and infrastructure challenges, no organized cervical cancer screening programs exist in Mali. Because Mali is one of the countries with the lowest socioeconomic status [7], resources to implement a vaccination program are lacking; most implemented vaccination programs are subsidized by external organizations. Despite available vaccines (eg, Gardasil Access program), challenges in implementing vaccines remain owing to widely dispersed populations and limited infrastructure to support a multidose vaccination campaign. Consequently, it is a public health necessity to evaluate probable impacts of a vaccination program during pre-implementation planning.

HPV mathematical models exist; however, none directly apply to developing countries. Previous models focus almost exclusively on developed countries [8–11]. Demographic, cultural, and economic differences among countries along the economic development continuum imply that existing models will not provide necessary estimates and insight for planning and implementation of an effective vaccination program in a country such as Mali. For example, the model for HPV transmissibility developed by Burchell et al [8] was based on a university sample of unmarried and uncircumcised individuals able to form multiple sexual partnerships. In contrast, the female Malian population has an 89% probability of being circumcised (a known risk factor for cervical cancer [12]) and marries at an earlier age; nearly half are in a polygamous marriage. These factors, which might affect successful implementation of any HPV vaccination program, formed the basis of our mathematical models exploring the probable impact of HPV vaccination in Mali.

Purpose

To use mathematical models to evaluate the impact of a single vaccination campaign of all at-risk female individuals in Mali. We focused on common HPV types 16 and 18, which collectively account for ~70% of cervical cancer cases worldwide [13–15].

Received 21 July 2010; accepted 3 December 2010.

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Clinical Infectious Diseases 2011;52(5):641–645

1058-4838/2011/525-0001$37.00
DOI: 10.1093/cid/ciq190

METHODS

Model

We developed a deterministic mathematical model to evaluate the impact of vaccination and sexual mixing on predicted prevalence of HPV infection and cervical cancer incidence. This model of heterosexual HPV transmission dynamics followed developed models [16], dividing the population into 3 sexual activity and/or risk groups defined by differences in partner change rate.

Vaccination Strategies

Focusing on the at-risk Mali population (women aged ⩾11 years), we assessed vaccine coverage rates of 0%, 15%, 30%, 50%, and 90%, corresponding to ~1, 2, 3, and 5.5 million vaccine doses.

Sexual Mixing Patterns

Risk of HPV infection in susceptible women varies with age and sexual activity risk group, reflecting known heterogeneity in risk for acquiring sexually transmitted infections. Once infected, cervical cancer risk increases with duration of infection. Risk groups reflect low, medium, and high numbers of annual sexual partners and are proportional to HPV transmission risk. Sexual mixing data for the Malian population are lacking; therefore, we assessed random, partially assortative, and fully assortative mixing patterns. Random mixing assumes that individuals select sexual partners from all risk groups with equal probability; fully assortative implies partner selection in only the same risk group, whereas partially assortative represents a hybrid of partners selection with preference to partners from the same risk group [17, 18].

Study Population

The model population was based on 2007 Mali data comprising 12.3 million persons with a mean life expectancy of 50 years [5] (Table 1).

Parameter Estimates

Table 2 provides default values for Mali-specific parameters in the model, assuming that cervical carcinogenesis is similar for various populations. Parameters were derived from published literature and unpublished pilot research conducted by the senior author (JKT) that estimated local prevalence of high-risk HPV infection and assessed HPV infection risk factors in Malian women. Results from this pilot study suggest that 12% of Malian women had a prevalent infection with a cancer-causing HPV strain.

RESULTS

Results show increasing vaccination coverage significantly decreases total prevalence of HPV infection. For example, 15% vaccination coverage reduces the maximum prevalence of infection from 39% to 33%, whereas 90% coverage reduces the peak prevalence to 7% (Table 3). We explored the effect of different vaccination strategies on cervical cancer burden by modeling numbers of women predicted to have persistent HPV infection that could lead to cervical cancer (ie, women with disease) for each vaccination strategy. Figure 1 shows women with disease, by risk group, for each vaccination strategy, showing reductions in total numbers of women with disease proportional to vaccination coverage. Without vaccination, the 25-year cumulative incidence of cervical cancer is ~27 cases per 1000 persons, compared with 3 cases per 1000 persons with 90% coverage, corresponding to a relative reduction of 89% (Table 4).

Simulations assuming random mixing predicted the highest total prevalence of HPV infection, whereas fully assortative mixing predicted the lowest prevalence for all vaccination strategies. However, with 90% coverage, the negative effect of random mixing is negligible. In addition, the benefits of fully assortative mixing are not equal across risk groups. The greatest benefit occurs in the lowest risk group, whereas in the highest risk group, which includes pairing with other individuals at high risk, the model predicted a higher prevalence.

DISCUSSION

HPV vaccines offer an innovative strategy for cervical cancer control and prevention; however, knowledge of the real world impact of these vaccines remains in its infancy. Published

Table 1. Mali Population Estimates, by Risk Group

Risk Group, age, years	Population Size in 2007 [28], no. (%)		Prevalence/person [28]		No. Infected at T0		No. Susceptible at T0	
	Male	Females	Male	Female	Male	Female	Male	Female
<15	3,320,765 (0.531)	3,198,961 (0.519)	0.0001	0.0001	332	320	3,320,433	3,198,641
15–24	1,393,195 (0.223)	1,353,382 (0.219)	0.17	0.17	236,843	230,075	1,156,352	1,123,307
25–50	1,540,562 (0.246)	1,616,803 (0.262)	0.3	0.15	462,169	242,520	1,078,393	1,374,283
All	6,254,522	6,169,146			699,344	472,915	5,555,178	5,696,231

Table 2. Model Parameters[a]

Model Parameters	Parameter	Value(s)	Source
Female individuals			
Proportion vaccinated	ϕ_f	[0,1]	Assumed
Annual cervical cancer rate	τ	0.01	Bayo et al [12]
Annual cervical cancer mortality rate (age standardized)	Ca_D	28.4 deaths/100,000 population	WHO HPV and CC summary report, 2007(28)
Probability of HPV transmission from infected man	β_f	0.8	
Men			
Proportion vaccinated	ϕ_m	[0,1]	Assumed
Probability of HPV transmission from infected female	β_m	0.7	
Both sexes			
Annual mean duration in risk group	$1/u$	[10 10 15]	
Proportion in risk group	ω	[.53 .22 .25]	
Annual sexual partners	π	[.7 5.2 10.1]	
Annual mortality rate (background)	δ	0.016	CIA Fact book [5]
Mixing parameter	ϵ	[0 1]	Assumed
Duration of infectiousness	$1/\gamma$	0.15	Hughes et al [16] (29–31)

[a] Risk group 1: <15 years; risk group 2: 15–24 years; risk group 3: >25 years.

mathematical models are based on theoretical assumptions using data prior to vaccine licensures and almost exclusively included parameter estimates derived from data for developed countries. Thus, the impact of HPV vaccination in developing countries is unknown. Using Mali-specific assumptions and parameter values, we assessed the impact of several single vaccination scenarios on HPV infection. Our findings suggest that reduction in peak prevalence of high-risk HPV infection is directly proportional to vaccination coverage, with the maximum reduction of 82% in peak prevalence with 90% coverage.

We explored the impact of vaccination strategies on cervical cancer burden by tracking numbers of women predicted to have persistent high-risk HPV infection that could lead to cervical cancer. Similar to our findings of vaccination effect on peak prevalence, reductions in numbers of women with disease were observed for each risk group with increasing vaccination coverage, with a relative reduction of up to 89% at 90% coverage

Finally, our models predicted that, for all coverage scenarios, random sexual mixing patterns resulted in the highest total prevalence of HPV infection, and fully assortative mixing resulted in the lowest peak prevalence, although the negative effect of random sexual mixing is negligible with 90% coverage. Furthermore, the benefits of fully assortative mixing are not uniform across risk groups.

Similar to other studies [16], our models suggest that population and vaccine program characteristics affect prevalence of HPV infection and prevalence of persistent HPV infection. Diaz et al [19] modeled the impact of HPV vaccination on cervical cancer prevention in India, reporting a 44% reduction with 70% vaccination coverage. In contrast, we focused on reduction in HPV infection, as the first step in the carcinogenesis pathway, and estimated a relative reduction in prevalence of HPV infection approaching 50% with 50% coverage. Our analyses reveal the importance of country- and culturally specific parameters,

Table 3. Comparison of Reduction in Prevalence for 4 Vaccine Scenarios, Compared with No Vaccine

Scenario, coverage	Peak Prevalence, %	Absolute reduction in prevalence, compared with no vaccine, %	Relative reduction in prevalence, compared with no vaccine, %
None	39	0	…
15%	33	6	15
30%	28	11	28
50%	20	19	49
90%	7	32	82

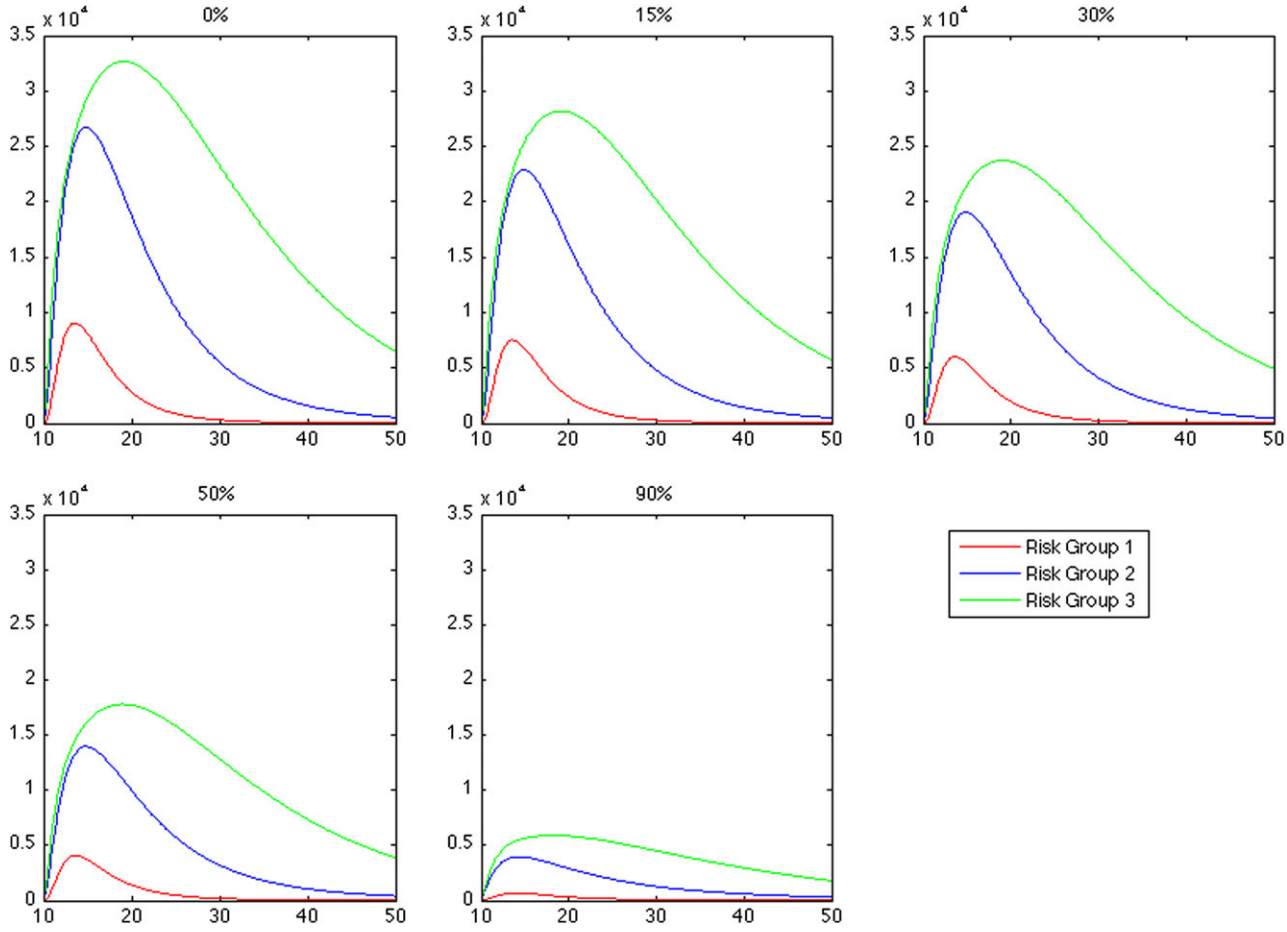

Figure 1. Prevalence of persistent human papilloma virus (HPV) infection, by risk group, for each vaccination strategy.

which differ across populations, to evaluate the probable impact of vaccine implementation.

HPV vaccines are designed to prevent cancer associated with viral infection; however, the long-term value of these vaccines is tempered by several critical issues. First, although current vaccines target the HPV strains that account for ~70% of cervical cancers worldwide, other cancer-causing strains circulate in the population and require continued screening. [20]. Second, vaccinating young women before HPV exposure (ideally before their sexual debut) presents unique economic, cultural, and logistical challenges.

Mathematical models of HPV infection are inherently limited by the extant knowledge and understanding of HPV infection. The simulations reported here include relevant parameters previously defined for models of developed countries. Future studies will explore culture-specific factors influencing this dynamic process, interactions between HPV strains, and vaccine cost-effectiveness in developing countries. Our research and future analyses can guide implementation of HPV vaccination in resource-poor settings to effectively reduce total burden of HPV infection and cervical cancer–related deaths.

Table 4. Reduction in Cumulative Incidence of Cervical Cancer at 25 Years, Compared with No Vaccine

	Vaccination Coverage				
Variable	0%	15%	30%	50%	90%
Cumulative Incidence at 25 years/person	0.027	0.023	0.018	0.013	0.003
Absolute Reduction in Cumulative Incidence/person, %	…	0.4	0.9	1.4	2.4
Relative Reduction in Cumulative Incidence/person, %	…	14.8	33.3	51.8	88.9

Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Child Health and Human Development, Office of Research on Women's Health, National Institute of Allergy and Infectious Disease, or the National Institutes of Health.

Financial support. This work was supported in part by the University of Maryland School of Medicine, National Institute of Child Health and Human Development and Office of Research on Women's Health (K12 HD43489) to J.K.T., and National Institute of Allergy and Infectious Diseases, National Institutes of Health (K25 AI067792) to H.D.G.

Potential conflicts of interest. P.E.G. is a board member of Qiagen, which manufactures HPV tests. All other authors: no conflicts.

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