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Cost-effectiveness analysis of introducing universal human papillomavirus vaccination of girls aged 11 years into the National Immunization Program in Brazil

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ABSTRACT

Objectives: To evaluate the impact and cost-effectiveness of introducing universal human papillomavirus (HPV) vaccination into the National Immunization Program (NIP) in Brazil.
Methods: The Excel-based CERVIVAC decision support model was used to compare two strategies: (1) status quo (with current screening program) and (2) vaccination of a cohort of 11-year-old girls. National parameters for the epidemiology and costs of cervical cancer were estimated in depth. The estimates were based on data from the health information systems of the public health system, the PNAD 2008 national household survey, and relevant scientific literature on Brazil. Costs are expressed in 2008 United States dollars (US$), and a 5% discount rate is applied to both future costs and future health benefits.
Results: Introducing the HPV vaccine would reduce the burden of disease. The model estimated there would be 229 deaths avoided and 6677 disability-adjusted life years (DALYs) averted in the vaccinated cohort. The incremental cost-effectiveness ratios (ICERs) per DALY averted from the perspectives of the government (US$ 7663), health system (US$ 7412), and society (US$ 7298) would be considered cost-effective, according to the parameters adopted by the World Health Organization. In the sensitivity analysis, the ICERs were most sensitive to variations in discount rate, disease burden, vaccine efficacy, and proportion of cervical cancer caused by types 16 and 18. However, universal HPV vaccination remained a cost-effective strategy in most variations of the key estimates.
Conclusions: Vaccine introduction could contribute additional benefits in controlling cervical cancer, but it requires large investments by the NIP. Among the essential conditions for attaining the expected favorable results are immunization program sustainability, equity in a population perspective, improvement of the screening program, and development of a surveillance system.

1. Introduction

Human papillomavirus (HPV) vaccines were first licensed in 2006, with the approval of Gardasil (Merck, quadrivalent, including HPV types 6, 11, 16, and 18) and of Cervarix (GlaxoSmithKline, bivalent, including HPV types 16 and 18). After that step, recommendations for vaccine introduction were developed by health authorities in European Community high-income countries, North America, and Australia. By the end of 2011, at least 37 countries had introduced an HPV vaccine into their National Immunization Program (NIPs) [1]. In the Americas, by the end of 2011, six countries (United States, Canada, Mexico, Panama, Peru, and Argentina) had introduced the vaccine, and other nations

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had approved their incorporation into their NIPs (Guyana and Suriname) [2,3].

In Brazil, Gardasil was registered with the National Agency for Sanitary Surveillance (*Agência Nacional de Vigilância Sanitária – ANVISA*) in 2006, and Cervarix in 2008. After their licensure, the vaccines became available in private immunization clinics. At the same time, medical associations intensified their pressure on the Ministry of Health (MoH) to incorporate the vaccine into the country's NIP. However, reports produced by public health institutions slowed vaccine introduction into the NIP, due to issues regarding the long-term vaccine effectiveness and population impact, prioritization of cervical cancer screening and treatment, the high cost and budget impact of the vaccine, and the need to develop special strategies for its delivery [4].

In 2008, the MoH launched a call for proposals for HPV cost-effectiveness studies. In 2012, preliminary findings from the research described in this article were presented to the Brazilian government [5], and the decision to introduce HPV vaccine into the NIP was announced by the MoH.

In March 2014, the quadrivalent HPV vaccine was introduced into the NIP in a school-based program. In 2014, the program targeted girls aged 11–13; in 2015, girls aged 9–11 years will be vaccinated, and from 2016, the vaccine will be administered to 9-year-old girls. An extended schedule (0, 6, and 60 months) was adopted.

This study evaluates the impact and cost-effectiveness of introducing universal HPV vaccination into the NIP in Brazil. Epidemiological, health resource utilization, and cost estimates were based predominantly on national health information systems data. The CERVIVAC decision-support model was used to estimate health impact and cost-effectiveness. This tool was developed by the ProVac Initiative of the Pan American Health Organization (PAHO). This PAHO initiative has worked to strengthen countries' decision-making regarding the introduction of new vaccines, particularly rotavirus, pneumococcal conjugate, HPV, and *H. influenzae* type b (Hib) in the Latin American and Caribbean region [6]. Cost-effectiveness is calculated by comparing HPV vaccination at age 11 years with the status quo (no HPV vaccination), and with both scenarios assuming no changes in current or future cervical cancer program screening and treatment practices. The study uses freely accessible recent national data and a transparent model that provides a consistent basis for international comparisons with other countries of Latin America and the Caribbean.

2. Methods

2.1. The CERVIVAC model

CERVIVAC is an Excel-based decision support model that tracks a single cohort of pre-adolescent girls over their lifetime. Numbers of cervical cancer cases and deaths are estimated by multiplying the number of women alive at each age with national estimates of disease incidence and mortality. Cervical cancer cases are divided into local and regional categories, with different disability weights assigned to each. The model estimates the number of cases, deaths, and disability-adjusted life years (DALYs) expected to occur over a lifetime for one cohort of girls. Total cancer treatment costs are estimated by multiplying the total number of cervical cancer cases in each age group by the average costs of receiving treatment in the public and private sector. We did not assume any preferential age weighting for the working age range. The impact of vaccination (number of cases, deaths, and DALYs averted) is calculated by multiplying the number of cervical cancer cases and deaths by: (a) the expected coverage of the vaccination program; (b) the proportion of cervical cancers that are likely to be prevented by the types (types 16 and 18) included in the vaccine; and (c) the anticipated long-term efficacy of the vaccine.

The model does not take into account the effect of the HPV vaccine on the male population, unvaccinated individuals, genital warts, or other cancers.

2.2. Strategies compared

This model compared two strategies: (1) no vaccination and (2) vaccination of a cohort of 11-year-old girls, using a three-dose vaccination schedule. In both scenarios, the model assumes no changes in current or future cervical cancer program screening practices. The cervical cancer screening strategy adopted in Brazil currently offers free Pap smear testing for the female population aged 25–64 years. The recommendation for the screening interval is every 3 years after two consecutive negative annual exams [7]. Diagnosis and treatment of precancerous lesions are provided freely by the public health sector.

The base case analysis did not consider catch-up of various cohorts of girls or boys, or any additional vaccine booster doses. The average cost-effectiveness of HPV vaccination is calculated in terms of the cost per DALY averted, cost per case averted, and cost per death averted.

In the cost-effectiveness analyses of introducing HPV vaccine 16 and 18 (without differentiation between Gardasil or Cervarix) against cervical cancer, the government, health system, and society perspectives were adopted. The government perspective included only direct medical costs of the public health system (*Sistema Único de Saúde, SUS*). The health system perspective included direct medical costs of both the public (SUS) and the private health systems. The society perspective included the direct medical costs, direct non-medical costs (transportation expenses), and indirect costs of lost productivity. The time horizon used in the analysis was 100 years. The costs are expressed in 2008 United States dollars (US$) at the exchange rate of US$ 1.00 = R$1.83 [8]. A 5% discount rate is applied to both future costs and future health benefits [9].

2.3. Epidemiological and disease burden estimates

The incidence and mortality rates for cervical cancer were based on national studies with adjusted data from the Mortality Information System (*Sistema de Informações de Mortalidade, SIM*) and population-based cancer registries [10–12] (Table 1).

The estimated percentage of cases of cervical cancer diagnosed in stages I, II, III, and IV and the 5-year survival rate of each stage were based on data from the Hospital Cancer Registry of the State of São Paulo, the largest good quality available database [13].

The disabilities weights for stages I, II, III, and IV used to calculate disability-adjusted life years (DALYs) were based on disease burden estimates of the WHO [14,15].

2.4. Health service utilization and costs for the treatment of cervical cancer estimates

Estimates of access to medical treatment were based on information provided by the MoH and estimates of a Brazilian population survey, the National Survey of Household Samples (*Pesquisa Nacional por Amostra de Domicílios – PNAD Saúde 2008*) [16] (Table 2).

Estimates were grouped into sets of procedures performed in cervical cancer treatment care, according to specialized publications and clinical guidelines [17]. Costs were estimated for both the public and private health systems (Table 2).

Costing was performed using "gross costing" or "top-down" methodology, where costs represent national averages actually