Papillomavirus Research 1 (2015) 38–58

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

When and how often to screen for cervical cancer in three low- and middle-income countries: A cost-effectiveness analysis

Nicole G. Campos [a,*], Vivien Tsu [b], Jose Jeronimo [b], Mercy Mvundura [c], Kyueun Lee [a], Jane J. Kim [a]

[a] Center for Health Decision Science, Harvard T.H. Chan School of Public Health, 718 Huntington Avenue, Boston, MA, USA
[b] PATH, Reproductive Health Global Program, PO Box 900922, Seattle, WA, USA
[c] PATH, Devices and Tools Program, PO Box 900922, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 28 April 2015
Received in revised form
26 May 2015
Accepted 27 May 2015
Available online 15 June 2015

Keywords:
Cancer screening
Human papillomavirus (HPV)
Cervical cancer
Cost-effectiveness analysis
Visual inspection with acetic acid

ABSTRACT

World Health Organization guidelines recommend that cervical cancer screening programs should prioritize screening coverage in women aged 30 to 49 years. Decisions about target ages and screening frequency depend upon local burden of disease, costs, and capacity. We used cost and test performance data from the START-UP demonstration projects in India, Nicaragua, and Uganda to evaluate the cost-effectiveness of screening at various start ages, intervals, and frequencies. We calibrated a mathematical simulation model of cervical carcinogenesis to each country and compared screening with *care*HPV (cervical and vaginal sampling), visual inspection with acetic acid (VIA), and cytology between the ages of 25 and 50 years, at frequencies of once to three times in a lifetime, at 5- and 10-year intervals. Screening with *care*HPV (cervical sampling) was the most effective and cost-effective strategy in all settings; *care*HPV (vaginal sampling) was only slightly less effective. The most critical ages for screening are between ages 30 and 45 years. Within this age range, screening at certain ages may be relatively more cost-effective, but cancer risk reductions are similar for a given screening test and interval. Screening three times between 30 and 45 years was very cost-effective and reduced cancer risk by ~50%.

1. Introduction

Cervical cancer is the fourth most common cancer in women, resulting in an estimated 528,000 incident cases and 266,000 deaths worldwide in 2012 [1]. Approximately 85% of cases and deaths occur in the developing world, where the implementation of cytology-based screening programs to detect and treat precancerous lesions do not exist, or they have not been effective due to lack of health delivery infrastructure and limited financial resources [2]. Despite the difficulties of implementing organized screening programs, several clinical and economic studies have suggested that one- and two-visit screen-and-treat approaches using visual inspection with acetic acid (VIA) or human papillomavirus (HPV) DNA testing can be feasible, beneficial, and cost-effective in low-resource settings [3–6]. HPV DNA testing is associated with higher sensitivity than VIA to detect precancer [7–9], yet VIA is associated with programmatic advantages, including lower costs and the ability to screen and treat within a single visit. A public–private collaboration has led to the development of *care*HPV (QIAGEN, Gaithersburg, MD), a lower-cost DNA test that can be used in clinics that lack reliable clean water or electricity; the performance of *care*HPV has been validated in demonstration projects and it has been shown to be cost-effective when part of a screen-and-treat algorithm in El Salvador [10].

The World Health Organization (WHO) recommends that screening begin at 30 years of age, with priority given to maximizing population screening coverage of women aged 30 to 49 years rather than maximizing the number of screening tests in an individual woman's lifetime [11,12]. Recommended screening tests include HPV testing and VIA, with suggested rescreening intervals of 3 to 5 years following a negative VIA screening result, and no less than 5 years following a negative HPV test [11,12]. Where high quality cytology (i.e., Pap) programs are already in place, cytology may be used as a screening test [11]. For HIV-infected women or women with unknown HIV status in high endemic areas, rescreening following a negative screening test is recommended within 3 years [11,12]. The WHO guidelines state that screening even once in a lifetime is beneficial, and intervals may depend on available

Abbreviations: CIN, cervical intraepithelial neoplasia; GDP, gross domestic product; HPV, human papillomavirus; I$, international dollar; ICER, incremental cost-effectiveness ratio; VIA, visual inspection with acetic acid; WHO, World Health Organization; YLS, year of life saved

* Corresponding author at: 718 Huntington Avenue, Boston, MA 02115, USA. Tel.: +1 617 432 2019; fax: +1 617 432 0190.
E-mail address: ncampos@hsph.harvard.edu (N.G. Campos).

http://dx.doi.org/10.1016/j.pvr.2015.05.003

resources and infrastructure; decisions about the target ages and frequency of screening depend upon local burden of disease, costs, and infrastructure, and are left to country-level decision makers [12].

In settings where screening may only take place once, twice, or three times in a woman's lifetime, decision makers need information on the optimal screening ages and intervals to maximize the health benefits and value associated with limited screening opportunities. Using cost and test performance data from the Screening Technologies to Advance Rapid Testing–Utility and Program Planning (START–UP) demonstration projects in India, Nicaragua, and Uganda, our objective was to evaluate the cost-effectiveness of screening at various start ages, intervals, and frequencies in resource-limited settings with different epidemiologic profiles.

2. Material and methods

2.1. Analytic overview

We used an existing individual-based Monte Carlo simulation model of the natural history of HPV and cervical cancer to estimate lifetime health and economic outcomes associated with screening with HPV DNA testing, VIA, and cytology at selected ages and intervals [10,14–17]. The model was calibrated to epidemiologic data from India, Nicaragua, and Uganda. Test performance and cost data were drawn from the START–UP multi-site demonstration project conducted in India (Hyderabad), Nicaragua (Masaya Province), and Uganda (Kampala) [7,18]; a fourth site in India was not included in this evaluation. Model outcomes included lifetime risk of cervical cancer, total lifetime costs (in 2011 international dollars [I$]), and life expectancy. Cost-effectiveness ratios were expressed using incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a particular strategy divided by its additional health benefit, compared with the next most costly strategy after eliminating strategies that are dominated (defined as more costly and less effective, or having higher ICERs than more effective options). While there is no universal criterion that defines a threshold cost-effectiveness ratio, we considered the heuristic that an intervention with an ICER less than the country's per capita gross domestic product (GDP) would be "very cost-effective" and less than three times per capita GDP would be "cost-effective"[19]. In addition to value for money, we estimated the financial costs of screening to determine a country's budget impact over a 1-year period. Consistent with guidelines for cost-effectiveness analysis [20–22], we adopted a societal perspective, including costs irrespective of the payer, and discounted future costs and life-years at a rate of 3% per year to account for time preferences.

2.2. Mathematical simulation model

The natural history model of cervical carcinogenesis in an individual woman is represented as a sequence of monthly transitions between mutually exclusive health states, including type-specific HPV infection status, grade of precancer (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3), and stage of invasive cancer [10,14]. Transition probabilities may vary by age, HPV type, duration of infection or precancerous lesion status, and prior HPV infection. Cancer detection can occur through symptoms or via screening. Each month, death can occur from non-cervical causes or from cervical cancer after its onset. The model tracks disease progression and regression, clinical events, and economic outcomes over the lifetime for each individual woman, which are then aggregated for analysis.

Details of the model parameterization process, including calibration, have been previously published [10,14,15] and are described in the Appendix. Briefly, we estimated baseline "prior" input parameter values for natural history transitions using longitudinal data [23–27]. To reflect heterogeneity in age- and type-specific HPV incidence between settings, as well as natural immunity following initial infection and uncertainty in progression and regression of precancer, we set plausible ranges around these input parameter values. Repeated model simulations in the absence of any intervention selected a single random value from the plausible range for each uncertain parameter, creating a unique natural history input parameter set. We then computed a goodness-of-fit score by summing the log-likelihood of model-projected outcomes for each unique parameter set to represent the quality of fit to country-specific epidemiologic data (i.e., calibration targets). For each country, we selected the top 50 input parameter sets that produced good fit to the epidemiologic data to use in analyses as a form of probabilistic sensitivity analysis [14,15,28]. Model fit to empirical data on age-specific high-risk HPV prevalence data from the START–UP projects and age-specific cancer incidence is displayed in the Appendix. We report results as the mean and range of outcomes across these top 50 parameter sets; incremental cost-effectiveness ratios are reported as the ratio of the mean costs divided by the mean effects of one strategy versus another across sets [29].

2.3. Strategies

We assumed available screening tests included *care*HPV (provider-collected [cervical] and self-collected [vaginal] sampling), VIA, and conventional cytology, with site-specific test performance parameters informed by the START–UP demonstration projects. Self-collection of vaginal HPV samples does not require pelvic evaluation, and thus was evaluated as an alternative to provider-collection. Test performance and treatment parameters are presented in Table 1 [7,30–36]. For VIA, we assumed that women who were screen-positive and eligible for cryosurgery were generally treated at the same clinical visit but that a proportion refused immediate treatment and either returned for a subsequent visit or was lost to follow-up; for those not eligible for cryosurgery, we assumed referral to a secondary facility for further diagnostic testing and treatment. For *care*HPV testing, we assumed women were screened during the first visit and returned for a second visit to obtain results; if they screened positive and were eligible, most received same-day cryosurgery. Cytology included an initial visit for screening, a second visit to receive results, a third visit to receive diagnostic colposcopy and biopsy for screen-positive women, and if necessary, a fourth visit for treatment. Treatment protocols for women who were not eligible for immediate cryosurgery, and management following treatment, were based on current practice in each country and are documented in the Appendix.

To focus on the ages recommended by the WHO as well as ages when opportunistic screening may occur, we evaluated each screening test at the following frequencies, ages, and intervals: (1) once in a lifetime at ages 25, 30, 35, 40, 45, or 50 years; (2) twice in a lifetime at ages 25 and 35 years; 30 and 40 years; or 35 and 45 years; and (3) three times in a lifetime at ages 25, 35, and 45 years; 30, 35, and 40 years; 35, 40, and 45 years; or 30, 40, and 50 years. At each target age in a given screening strategy, the model randomly selected 70% of women for screening. Thus, for screening at later ages in strategies involving two or three screenings in a lifetime, women did not have to have been screened previously in order to be selected for screening at a later target age.

2.4. Cost data

Cost data (in 2011 I$) are presented in Table 1. Direct medical costs of screening, diagnosis, and treatment of precancerous lesions were drawn from the START–UP study sites, and included staff time, clinical supplies, drugs, clinical equipment, laboratory staff time, laboratory