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Cost-Effectiveness of HPV-Vaccination in Medium or Low Income Countries with High Cervical Cancer Incidence – A Systematic Review

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Abstract

Background: Prophylactic human papilloma virus (HPV) vaccines represent a promising option for cervical cancer (CC) prevention in countries where screening, diagnostics and treatment have difficulties in producing significant reductions in CC incidence/mortality. Numerous studies have evaluated the cost-effectiveness of HPV vaccination strategies including female vaccination alone, female vaccination combined with different screening strategies, or female and male vaccination. Countries with the highest CC incidences, however, have the least resources to implement any CC prevention programs. To understand priorities in low *vs.* middle income countries with high CC incidence pertinent cost-efficacy studies on CC interventions were compared.

Methods: We conducted a systematic review of cost-effectiveness studies including only countries with high CC incidence (>14.5) and GDP per capita below the high income group (<37,162 2010 international $).

Results: We identified 16 cost-effectiveness studies (with the bivalent 16/18 or the quadrivalent 6/11/16/18 vaccine) including 25 countries from Europe, Africa, Latin America, and Asia. CC incidence ratios vary from 14.8 (Kenya) to 38.3 (Mozambique) and GDP per capita from 913 (Mozambique) I$ to 27063 I$ (Slovenia). High income countries that met the high CC incidence criteria included Ireland (14.7) and Denmark (18.4). Sub-Saharan African countries excluded, the CC incidence rates were comparable in the middle- and low-income countries (median 18.5 *vs.* 22). All of the studies concluded that HPV vaccination of females is very effective, especially combined with a screening, and cost-effective assuming a low to moderate vaccine price at the same time underlining that the commonly used cost-effectiveness thresholds do not always equal affordability.

Conclusion: Our systematic review showed that HVP vaccination alone or combined with screening strategies is cost-effective in countries with high CC incidence and moderate to low GDP per capita. Affordability of the vaccination program is a crucial determinant for the success of cervical cancer prevention by country, and determines whether rapidly increasing differences between the middle-and low-income countries in HPV disease burden are imminent in the future.

Keywords: HPV-vaccination; Anogenital cancers; Cervical cancer; Prophylactic vaccines; hrHPV infections

Introduction

Cervical cancer (CC) is the third most common cancer in women [1] and the most common cancer in women in several developing countries [2]. High-risk (hr) human papilloma virus infection is the necessary cause of cervical cancer, infections with [3] hrHPV types 16 and 18 being the most prominent causes [4,5]. It has also been established that hrHPVs cause significant proportions of other anogenital cancers (anus, vulva, vagina, and penis) and [2,6-13] head and neck cancers in both men and women.

Screening has resulted in significant decrease in the incidence of cervical cancer in developed countries whereas in developing countries the results have been marginal [2,14-21]. Prophylactic HPV vaccines available since late 2000's (FDA 2006; EMEA 2007) offer a promising way to prevent cervical cancer and other HPV related cancers both in the developed and in the developing countries. The licensed HPV vaccines were proven to be highly efficient against targeted hrHPV types 16 and 18 [22,23] which cause approximately 70% of cervical cancers worldwide [24] and the bivalent vaccine has also shown cross-protection against non-vaccine hrHPV types HPV-31, HPV-33, HPV-45, and HPV-51 [25]. Prophylactic vaccines need to be administered before the individuals are exposed to the virus and in the case of HPV this means vaccination before sexual onset.

Cost-effectiveness of any health intervention is one of the most important factors determining whether an intervention is to be implemented be it a developed or a developing country. Several cost-effectiveness studies have been published to determine the most effective way to prevent cervical cancer. Vaccination combined with organized screening [26-28] or vaccination alone [29,30] are often recommended as the most cost-effective overall strategies [26-81] even though in the latter case the role of any screening remains often undefined.

The cost-effectiveness threshold commonly used is country's per capita gross domestic product (GDP) based on a report by the Commission on Macroeconomics and Health. The WHO threshold is divided into 3 groups: highly cost-effective (less than GDP per capita), cost-effective (1-3 times GDP per capita), and not cost-effective (more than 3 times GDP per capita). These thresholds are commonly used in cost-effectiveness studies but they do not always reflect affordability.

Despite different inputs and assumptions about program settings

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most of the cost-effectiveness models have come to a same conclusion: the most cost-effective strategy is to vaccine females before sexual onset. Only a few studies suggest that including males in the vaccination strategy would be the most effective strategy [32,67]. Including males in the vaccination program appears more cost-effective/effective if it is assumed that the vaccination coverage in females were low [38,52,82].

To adopt the most cost-effective strategy in developing countries it is vital that any vaccine program implemented is population based. Among other model inputs there are several uncertainties including e.g. price of the vaccine, duration of immunity, transmission model used, targeted coverage, herd immunity effect, efficacy against different HPV types, efficacy against cervical cancer and other HPV-related cancers, and the role and costs of screening. Examining the cost-effectiveness model outputs for countries with high CC incidence and relatively low GDP we wanted to compare the assumptions made and evaluate their relevance in the light of newest findings.

Methods

Our aim was to study cost-effectiveness of HPV vaccination in developing countries with a heavy cervical cancer burden in fertile-aged women. The countries, where (or for which) cost-effectiveness evaluation of HPV vaccination has been done were selected according to two parameters: CC incidence [ages 15-49 ASR (W)] and GDP per capita, PPP (current international $ 2010). Information on the CC incidence was based on Globocan 2008 database on cancer incidence, mortality, and prevalence worldwide in 2008 [2,83] the average CC incidence of the world being 14.5 ASR (W). All the countries with CC incidence of 14.5 or higher were considered having heavy cervical cancer burden.

A systematic search of the international database Medline (Ovid) was conducted using medical subject headings (Mesh terms). The terms used were 'Papilloma virus Vaccines', 'Costs and Cost Analysis' and 'Cost-Benefit Analysis' and they yielded 239 results. Review articles, comments and editorials were excluded, as well as articles not providing incremental cost-effectiveness end points (per quality adjusted life years, QALY, per years of life saved, YLS, or per disability-adjusted life year, DALY, averted). This resulted in 75 studies regarding over a hundred countries. The number of studies was narrowed further using the predetermined factors, country specific CC incidence and GDP data, to establish the group of articles on cost-effectiveness of HPV vaccination in countries facing critical challenges in HPV infection and related disease prevention. Only papers in English and presenting country-specific results were included.

The index used to determine financial status of a country was GDP per capita (current international $ 2010, I$) and the data was retrieved from the World Bank database [84]. All the countries below the high income GDP per capita (37,162 2010 international $) were considered eligible.

Conflicts of interests were mentioned in three of the sixteen selected articles [53,67,75]. All three studies were funded by a vaccine manufacturer. In three other studies a part of the study was funded by a vaccine manufacturer which according to the statements did not influence design or conduct of the study and no conflict of interest was declared [56,66,76]. Seven of the studies [26,38,49,77-81] had received funding from a foundation and three declared no conflict of interest or external funding sources. Unless otherwise indicated, these peer reviewed studies are included in the systematic review.

The results of cost-effectiveness studies are expressed in ratios where the numerator represents the costs and the denominator the health benefits. The benefits can be expressed as QALYs gained or DALYs averted, life years saved (LYS), life years gained (LYG), or YLS. In our study LYS, LYG, and YLS are treated as equal and we represent LYS and LYG as YLS. The costs are most often represented in I$ to enable comparisons between countries.

Results and Discussion

Selection of the studies/countries

After applying the criteria on CC incidence and GDP the number of countries fulfilling both the criteria on heavy cervical cancer burden and moderate/low GDP was 25 (16 studies) [26,38,47,49,53,56,61,66,67,75-81]. In table 1 the countries are listed according to their CC incidence. There are great differences between the countries by both criteria. CC incidence of Mozambique is over 2.5 higher than that of Kenya and the GDP per capita (2010 international $) of Slovenia is almost 30 times higher than the GDP per capita of Mozambique.

According to GDP per capita and the income groups defined by the World Bank most of the countries (14) in our study can be characterized as low (1,274) or lower middle (3,517) income countries. Mozambique has the lowest (913) and Armenia the highest (5,439) GDP per capita among this group. Thailand and Peru are slightly below the upper middle income group (10,021) while the rest of the countries (7) slightly (South-Africa and Brazil) or significantly (Slovenia) above. Information was not available for Myanmar and Zimbabwe. While other measures had originally been used in the reviewed articles our

Population	Incidence	Incidence	GDP per capita
	Crude 15-49 yrs	ASR (W) 15-49 yrs	(current internatl $) 2010
Mozambique	32.3	38.3	913
Uganda	23.5	34.7	1275
Tanzania	25.7	33.6	1435
Zimbabwe	20.2	31.3	*
Peru	26.6	29.1	9538
Mongolia	25.6	28.3	4018
Nepal	22.8	26.7	1198
Lithuania	27.3	24.8	18184
Kyrgyzstan	22.5	23.9	2229
Myanmar	22.4	23.8	*
Hungary	22.7	22.2	20029
India	20.3	22	3582
Bangladesh	18	21.8	1652
Thailand	23.4	21.6	8516
Lao PDR	16.9	20.3	2567
Mexico	18.3	19.3	14498
Cambodia	16.1	18.8	2184
Brazil	18.3	18.5	11210
South African Republic	16.3	18.2	10570
Argentina	16.9	17.3	16012
Bhutan	13.8	17.2	5305
Pakistan	13	15.9	2676
Armenia	17.5	15.7	5439
Slovenia	16.5	15.4	27063
Kenya	11.3	14.8	1644

Table 1: Cervical cancer (CC) incidence (/100 000) in fertile-aged women and GDP per capita by country (World age-standardized rate. ASR. 14.5/100 000) [2.83]
*Data not available.

selection was based on GDP per capita in 2010 international dollars (I$, Annex).

It is noteworthy that two western European countries that represent the high-income group (GDP per capita above 37,162) had a CC incidence above the world average ASR and were subsequently excluded from our analyses. Denmark (GDP 40,178) had a relatively high CC incidence of 18.4 ASR (W) and Ireland (GDP 40,490) was just above the chosen CC incidence threshold (14.7). Furthermore, median and range of CC incidences in the upper-middle income group countries and low-income group countries were not remarkably different (18.5 *vs.* 22 per 100 000 person year) and excluding the sub-Saharan African countries, overlapped considerably (15.4-24.8 *vs.* 14.8-28.3), respectively.

It is even more noteworthy, that in most of the selected countries, the CC incidence is expected to rise significantly in the foreseeable future. In 2008 it was estimated that there are 255,741 (all ages) new CC cases in the selected countries. While the CC incidence has been predicted to decrease in the Nordic countries, which had adapted the organized screening in the 1970's [85], worldwide it is estimated that in 2030 the number of new CC cases will be 1.7 folded (436,568, all ages) simply because of demographic changes and assuming no changes in the background occurrence of hrHPV infections [83,86]. Furthermore, there is population-based evidence that the incidence/prevalence rate of e.g. HPV16 infections can double in 20 years in fertile-aged women with subsequent tripling of CC incidence in 11 years due to lack of attendance to organized screening [87,88]. Without any corrections in the background hrHPV prevalence in Lithuania, Hungary, and Slovenia the CC incidence has been estimated to remain unchanged or to decrease slightly, while in reality the opposite has happened [1,89]. It is likely that urbanization and lacking/poor possibilities to implement HPV mass vaccination in the selected low-income groups countries further enforces the epidemics and permits their occurrence in low income countries (Tables 2 and 3).

Low Income	1274
Lower Middle Income	3517
Middle Income	6756
Upper Middle Income	10021
High Income	37162

Annex: Income groups according to World Bank (Current international $ 2010).

Country	2008	2010	2030
Mozambique	3690	3877	5989
Uganda	3577	3768	7906
Tanzania	6241	6583	12016
Zimbabwe	1855	1869	3027
Peru	4446	4683	7712
Mongolia	335	357	609
Nepal	3504	3731	6731
Lithuania	511	507	464
Kyrgyzstan	673	700	1069
Myanmar	6434	6752	10501
Hungary	1086	1084	1042
India	134420	141768	226370
Bangladesh	17686	18933	35674
Thailand	9999	10465	13622
Lao PDR	491	522	923
Mexico	10186	10749	16579
Cambodia	1578	1672	2830
Brazil	24562	25935	41233
South African Republic	5743	5986	7710
Argentina	3996	4107	5421
Bhutan	50	54	97
Pakistan	11688	12448	23411
Armenia	385	390	474
Slovenia	151	153	153
Kenya	2454	2612	5005

Table 2: Actual and estimated numbers of new cervical cancer cases in 2008. 2010. and 2030 (all ages) [2].

Country	Urban (%)	Rural (%)	Population
Mozambique	31.0%	69.0%	23.39 M
Uganda	15.2%	84.8%	33.43 M
Tanzania	26.3%	73.7%	44.84 M
Zimbabwe	38.1%	61.9%	12.57 M
Peru	71.6%	28.4%	28.84 M
Mongolia	67.6%	32.4%	2.76 M
Nepal	16.7%	83.3%	29.96 M
Lithuania	67.2%	32.8%	3.32 M
Kyrgyzstan	35.3%	64.7%	5.33 M
Myanmar	32.1%	67.9%	47.96 M
Hungary	69.0%	31.0%	9.98 M
India	31.1%	69.9%	1181.41 M
Bangladesh	27.9%	72.1%	148.69 M
Thailand	33.7%	66.3%	69.12 M
Lao PDR	33.1%	66.9%	6.20 M
Mexico	77.8%	22.2%	108.55 M
Cambodia	19.8%	80.2%	14.14 M
Brazil	86.5%	13.5%	191.97 M
South African Republic	61.7%	38.3%	49.66 M
Argentina	92.4%	7.6%	39.88 M
Bhutan	34.8%	65.2%	0.73 M
Pakistan	35.9%	64.1%	173.59 M
Armenia	64.1%	35.9%	3.09 M
Slovenia	48.0%	52.0%	2.01 M
Kenya	23.6%	76.4%	40.51 M

Table 3: Population in urban and rural areas in 2010 [90].

Finally, we listed and categorized into Markov (M, 1-11) and dynamic (D, I-V) models all the cost-effectiveness studies included in our evaluation (Table 4). Briefly, while the Markov models considered direct protective effects on vaccinated/screened, the models categorized as dynamic transmission models also evaluated potential indirect effects of reducing HPV transmission to their partners.

Country-specific findings

Peru, Argentina, Brazil, and Mexico: Colantonio et al. [75] used a Markov cohort model [44] to conclude that HPV-vaccination program for 12-year-old females is cost-effective in these countries. They have different health care systems and differ also in terms of CC prevention. Their screening coverage has increased during the last decades but CC incidence is still relatively high. A common persistent problem is low screening coverage in the rural areas.

Local epidemiological, cost and health care-related data was used to reflect country specific profiles. Only common input was the natural history of CC which was modeled using probabilities reported in the literature. Coverage of a 3-dose vaccination regimen was assumed at 100% before sexual debut, and the protection gained was assumed for

1A. Peru [75]	2009	Markov state transition model. M
1B Argentina [75]	2009	Markov state transition model. M
1C Brazil [75]	2009	Markov state transition model. M
1D Mexico [75]	2009	Markov state transition model. M
2 Mexico [56]	2009	Markov cohort model. M
3 South African Republic [61]	2009	Markov cohort model. M
4 Slovenia [47]	2010	Markov cohort model. M
5 Thailand [76]	2012	Markov. M
6 Thailand [78]	2011	Semi-Markov. M
7 Kenya. Mozambique. Tanzania. Uganda. and Zimbabwe [80] 8 Armenia. Bangladesh. Bhutan. Cambodia. Kyrgyzstan. Lao PDR. Mongolia. Myanmar. Nepal. and Pakistan [81]	2012 2008	Empirically calibrated simulation model of cervical carcinogenesis. M A static cohort simulation model
9 India [26]	2008	Individual-based stochastic model. M
10 Brazil [49]	2007	Empirically calibrated simulation model of cervical carcinogenesis. M
11 Thailand [77]	2011	Empirically calibrated simulation model of cervical carcinogenesis. M
I Lithuania [66]	2011	Population-based transition model. D
II Hungary [53]	2010	Dynamic transmission model. D
III Brazil [38]	2007	Open cohort dynamic transmission model. D
IV Mexico [67]	2007	Dynamic transmission model. D
V Brazil [79]	2012	Dynamic individual-based model. D

Table 4: Cost-effectiveness models applied in the 25 countries.

lifetime. The model included (cross-) protection against HPV16/18 (HPV31, 60%, and HPV45, 78%). The cost per vaccinated female was estimated at 210 USD in the base case including costs of the vaccination program. All costs were presented in 2006 USD.

The authors compared cost-effectiveness of the current screening program and the current screening program combined with vaccination of 12-year-old females. The authors estimated country-specific Incremental Cost-Effectiveness Ratio (ICER) per quality-adjusted life year (QALY) saved. They considered an intervention as cost-effective when one QALY gained cost less than 3 times the country-specific GDP per capita. In all of the four countries adding vaccination to screening program was found to be cost-effective with following ICERs: Peru 4,576 USD, Argentine 5,964 USD, Brazil 10,181 USD, and Mexico 10,134 USD per QALY gained.

Mexico: Reynales-Shigematsu et al. [56] used a Markov model to analyze the cost-effectiveness of adding the quadrivalent HPV6/11/16/18 vaccine to an existing screening program in Mexico. A life-time protection and 100% vaccine coverage were assumed but the minimum vaccine coverage to yield a cost-effective ratio was 30%. With 100% vaccine coverage the incidence of cervical cancer could be decreased by 70%. The analysis was most sensitive to age of vaccination, duration of vaccine efficacy, and cost of vaccination.

The authors used Commission on Macroeconomics and Health definition of cost-effectiveness, that is, cost-effectiveness ratio less than the GDP per capita equals very cost effective. Using GDP per capita ($6,178 USD) as a threshold, vaccination alone is considered a very cost-effective strategy presuming that the cost of the vaccine is at $45 USD or lower and that the coverage is at least 30%.

They concluded that the vaccine-alone strategy once in a lifetime is the most cost-effective dominate strategy at $68 USD/LYS whereas one of the least cost-effective strategies was the conventional cytology test. Their analysis shows that the strategy of vaccination with screening every 3 years had the largest overall reduction (>75%) in cancer incidence and mortality at a cost of $15,935 USD/LYS compared with screening every 5 years. The authors, however, note that the most effective strategy might be a combination of screening and vaccination even though screening is not deemed cost-effective because of poor coverage [90].

South-Africa: Sinanovic et al. [61] developed a static Markov (state transition) model [43,91] incorporating both screening and vaccination. For the base-case scenario two strategies were compared: screening using conventional cervical cytology performed 3 times at 10-year intervals starting at age 30 and the same screening strategy with HPV vaccination for all 12-year-old females assuming 90% vaccine efficacy, 80% vaccine coverage, 100% completing their 3-dose regimen, and 50% getting the booster dose. If the vaccine costs US $192 (for 4 doses) or less vaccine plus screening strategy could be more cost-effective than screening alone.

The authors point out that vaccination could decrease diagnostic/treatment costs to the patient which is especially relevant in low-income countries. Using GDP per capita as a threshold for cost-effectiveness suggests that adding vaccination to the cervical cancer prevention program would be very cost effective even without discounted prices but from the point of view of affordability the costs without discounts do not seem acceptable, as is the case in many low-income countries. The price was estimated at US $480 for 4 doses including booster vaccination.

The ICER per years of life saved was used to evaluate the effect of adding HPV vaccination in the 2009 CC prevention program, and incremental QALY gained (compared with the current strategy- i.e. screening only). The ICER ranged from US $1078 per QALY gained to US $4,495 per YLS.

Slovenia: Cervical cancer is overall the fifth most common cancer in Slovenia (ages 15-49) and the third most common cancer in females (15-49) [2]. Obradovic et al. [47] demonstrate that HPV-vaccination alongside screening could be cost-effective in case the vaccine costs no more than 100 € per dose and offers a lifetime protection. The authors adapted a previously published and validated state transition Markov model [30,91,92] into Slovenian context. Screening was modeled according to the Slovenian screening program. In general terms women between 20 and 64 years are screened every 3 years. The program is based on cytology screening with a maximum of 3 visits (Pap smear, colposcopy, treatment). In the model it was assumed that the vaccine is administered in a school-based program, with two additional medical visits (GP).

The base case model assumed 80% vaccination coverage. In the base case the authors assumed 98% efficacy against infection with HPV16/18. A reduction of approximately 35% of CIN1 lesions, 51% of CIN2 and CIN3 lesions, and 66% of invasive cancer was assumed.

Vaccination was assumed to produce a protection for lifetime but the scenario in which a booster dose (fourth dose 10 years after the initial 3 doses) is needed was tested in a sensitivity analysis. In the booster scenario vaccination coverage was assumed to be 50% among the 22 year-old invited. In this case missing the fourth dose was considered to lose all the benefits of the vaccination, and HPV-vaccination would no longer be cost-effective. ICER including the booster strategy was 58,690 EUR per QALY. A hypothetical booster vaccination coverage of 100% and lowering discount rates from 5% to 3% or lower decreased the ICER value significantly (39 419 EUR per QALY for 100% coverage for the booster vaccination).

Thailand: Termrungruanglert et al. [76] developed a Markov simulation model to evaluate the cost-effectiveness of a HPV vaccination program using the quadrivalent vaccine compared with current standard practice (the clinical management of genital warts, CIN1, CIN2/3, and cervical cancer) in Thailand. The transitional probabilities were obtained from literature including data from Thailand. When country-specific data was unavailable the authors used data from The Asia-Pacific, other regions, and experts.

The assumptions concerning the HPV vaccination program included a 3-dose regimen at age of 12 with life-long protection and 100% vaccine coverage. The efficacy of the vaccine was estimated at 97% without cross-protection. It was assumed that treated and cured women return to healthy state with a possibility of a new similar diagnosis. Only health-care provider costs obtained from one large hospital were included.

In the base-case scenario the vaccine program was more expensive than current practice but resulted in greater QALY with an ICER of 4590 US$ per QALY (using exchange rate of 35 bahts per dollar). A sensitivity analysis showed that the price of the vaccine (340-430 US$ for three doses) would have to double or the coverage should fall under 80% in order to make the vaccination not cost-effective.

Thailand: Praditsitthikorn et al. [78] used a semi-Markov Model (transitional probability of moving from one health state to another is modeled as dependent of time since entry into a state) on the natural history of CC to compare the cost-effectiveness of female HPV 16/18 vaccination at age 15 to that of conventional cytology screening and screening using visual inspection with acetic acid (VIA).

The data for parameterization of the model was obtained from previous publications, country-specific surveys, reports, and registries. Both the healthcare provider and the societal perspective were included. The vaccine price used was 15000 Bt per 3 doses (1200 I$) without including administrative costs, which is considerably higher than most cost estimates in developing or developed countries. ICER of vaccinating 15 year old girls (coverage 100%) compared to the current national policy of screening women aged 30 to 65 every five years was estimated at 181000 Bt (14300 I$). Under no assumptions due cost-effectiveness was documented for prophylactic vaccination, and VIA or conventional screening were recommended instead.

Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe: Campos et al. [80] applied a simulation model of cervical carcinogenesis [49] to estimate the cost-effectiveness of CC prevention strategies in Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe. These countries represent the lowest GDP per capita in our study GDP per capita of Mozambique (410) being the lowest. Mozambique, Tanzania, Uganda, and Zimbabwe also represent the highest CC incidence in our study CC incidence of Mozambique [38.3 ASR (W)] being on top.

The strategies evaluated included both HPV-vaccination (females before age 12) and screening (HPV DNA testing once, twice, or three times per lifetime at ages 35, 40, 45). The model was calibrated with country-specific epidemiologic data when available. The cost estimates were based on country-specific data. In case of unavailability, cost data from other published sources was used.

In the baseline analysis 70% vaccine coverage was assumed for the first dose with an attrition rate of 15% for the second and the third dose, respectively. With three doses a full lifelong protection against HPV 16/18 was assumed (90% for two doses and 30% for one dose). HPV DNA testing was evaluated with different frequencies: 1-3 times in a lifetime, at ages 35, 40, and 45, respectively. One time VIA testing at age 35 was also considered.

Vaccination was more cost-effective than screening alone if the cost per vaccinated female was I$ 2 or below per dose. The ICERs were the following: Kenya 470 I$/YLS, Mozambique 250 I$/YLS, Tanzania 90 I$/YLS, and Uganda 130 I$/YLS (not reported for Zimbabwe). Screening alone became more attractive an option when the cost per dose was estimated at I$ 12.25 or more per dose. The most effective and still cost-effective option was vaccination followed by HPV DNA testing at age 35 provided that the cost per vaccinated female was between I$ 2 and I$ 5 per dose. The ICERs were 2,090 I$/YLS for Kenya, 1,260 I$/YLS for Mozambique, 740 I$/YLS for Tanzania, and 1,000 I$/YLS for Uganda.

Armenia, Bangladesh, Bhutan, Cambodia, Kyrgyzstan, Lao PDR, Mongolia, Myanmar, Nepal, and Pakistan: Goldie et al. [81] used two different models (an individual-based stochastic model and a static cohort simulation model) to assess cost-effectiveness of HPV 16/18 vaccination in 25 countries in Asia eight of which met the criteria in our study. The individual-based empirically calibrated micro-simulation model was used to assess cost-effectiveness in countries where sufficient epidemiological data was available. The static model was used elsewhere. The latter is a simplified model and does not fully simulate the natural history of HPV infection and cervical cancer.

The results indicate that assuming a very low cost per vaccinated female (I$ 10) the ICER expressed in I$/disability-adjusted life year (DALY) averted is I$ 70 for Armenia, I$ 50 for Bangladesh, I$ 60 for Bhutan, I$ 50 for Cambodia, I$ 70 for Kyrgyzstan, I$ 180 for Lao PDR, I$ 160 for Mongolia, I$ 40 for Myanmar, I$ 70 for Nepal, and I$ 500 for Pakistan. The ICERs indicate that the HPV vaccination would be very cost-effective given that the vaccine price would be low. Even at the price of I$ 50 per vaccinated female the ICERs still indicate that the vaccination is cost-effective in most of the included countries. The ICERs range from I$ 2,970/DALY averted for Pakistan to I$ 560/DALY averted for Bangladesh.

India: CC is the most common cancer, also in ages 15-49 in India. Diaz et al. [26] used an individual-based stochastic model [49,93] to simulate different screening strategies including also non-targeted HPV-types in their analysis of CC prevention in India.

Coverage of 70% with the 3-dose regimen was assumed in the base case analysis. The authors assumed a life-long protection against HPV 16 and 18, but no cross-protection against other hrHPV types. The authors used a composite value, the 'cost per vaccinated female' from I$ 5 to I$ 360 (I$ 2005) to evaluate the costs of the vaccination strategy. (Example: a composite cost of I$ 10 per vaccinated female consists of three doses of vaccine at $ 2.00 each; wastage of $ 0.90; freight and supplies of $ 0.59; administration of I$ 0.50; and incremental programmatic costs for immunization services, and incremental costs of social mobilization and outreach of I$ 2.00). No assumptions about differential operational capacity to deliver the vaccine were made.

At a cost per vaccinated female of I$ 10 or less (per dose approximately $2) vaccination alone was preferable to screening alone. A combined approach of pre-adolescent vaccination and screening 3-times per lifetime (at the ages of 35, 40, and 45) using visual inspection (VIA) cost I$ 290 per YLS and was also considered very cost-effective. The price of the vaccination being over $ 10 the most effective option would be to combine vaccination with three times per lifetime screening (VIA or HPV DNA testing). The combination was found to be most effective but may not be applicable in all regions in India. With VIA and HPV DNA screening available or with only HPV DNA screening available, the ICER for vaccination alone was cost saving if cost per vaccinated female was assumed at I$ 10. With only HPV DNA testing available screening alone or a combined approach became more cost-effective as the price per vaccinated female exceeds I$ 30 per vaccinated female (the ICER of vaccination alone being I$ 390/YLS compared to I$ 1780/YLS of the combined strategy).

Brazil: In Brazil CC is the second most common cancer (ages 15-49). 2 According to Goldie et al. [49] HPV-vaccination would be very cost-effective in Brazil if the cost per vaccinated woman is less than I$ 25 (dose I$ 5). In the most effective scenario vaccination would be followed by screening three times per lifetime between ages 35 and 45. This estimation was based on coverage of 70% on both interventions. For the authors, the main questions concern achieving high coverage, that is, how realistic the chosen strategy is. They also point out that it is unknown what kind of correlation there will be between screening and vaccination behavior (clustering of attendees and rejection). The natural history of HPV is considered (type-specific transmission by age and sex, immunity following natural infection, clearance and re-infection or reactivation predominates by age) but sexual behavior data is limited. The ICER expressed in I$/YLS for vaccination only was cost saving if the cost per vaccinated female was at I$ 25, and close to cost-neutral (I$ 300/YLS) if the cost per vaccinated female was I$ 50.

Thailand: Sharma et al. [77] evaluated cost-effectiveness of CC prevention strategies in Thailand using an empirically calibrated simulation model [49]. The authors found that most CC prevention strategies are below the commonly used cost-effectiveness threshold of GDP per capita. A lower cost-effectiveness threshold of approximately I$ 3340 (instead of GPD per capita) was also used to better reflect the affordability of different strategies.

According to this study vaccination combined with VIA screening five times per lifetime would be the most effective strategy with a ratio under the lower threshold but in this scenario the costs per vaccinated female should be I$ 50 or below. At higher costs for vaccination screening alone (5×HPV testing) is more cost-effective. The study shows that with low-cost vaccines (cost per vaccinated girl at I$ 10 or below) HPV vaccination alone is cost saving compared to no intervention.

The ICERs expressed as cost per YLS for vaccination only varied from cost saving to 2400 I$ cost per vaccinated girl ranging from 10 to 100 I$. At the same cost range the ICERS for vaccination and cytology three or five times per lifetime were $ 4830 and $ 5670, respectively. Costs are presented in 2005 I$.

Lithuania: Vanagas et al. [66] compared the cost-effectiveness of vaccinating 12-year-old or 15-year-old females at different levels of vaccination coverage. The authors used a population-based health state-transition model which differed from the Markov cohort and other dynamic models applied in other studies. Their model tracks several cohorts and the population changes over time as individuals enter and exit the model. Their model does not have a natural end-point. This model presumes a possible reduction in the population prevalence of HPV over time resulting in the reduced likelihood of infection in the long run via herd-immunity.

Varying the level of coverage of 3-dose vaccination regimen with HPV16/18 vaccine efficacy estimates between 90–100% over time was evaluated. The authors used age- and disease stage-specific epidemiological data from the Lithuanian Cancer Register. Only direct medical costs were included and the estimate prices for screening and diagnoses were derived from the National Sickness Fund healthcare claims registry. All costs were expressed in 2007 Euros.

The authors predict up to 76.9% overall reduction in CC incidence, 80.8% reduction in CC morbidity, and 77.9% reduction in CC mortality over a lifetime for the vaccinated female cohorts. However, they also predict further benefits resulting from herd-immunity which, according to the model used, would be significant even if only small proportions of the population were vaccinated. The study predicted only small differences between the two strategies (vaccination of 12- or 15-year-old girls) compared, but state that in terms of cost per life year gained (LYG) a population-based vaccination program for 15-year-old females would be more cost-effective.

The assumed herd-immunity effect from 30% coverage in a female-only vaccination strategy is questionable [94,95]. The authors took into account only hrHPV types 16 and 18 hence disregarding any vaccine induced cross-protection [80] or protection against HPV types 6 and 11 targeted by the quadrivalent vaccine. The model did not include assumptions about possible changes in the incidence of cervical cancer, undetected cervical cancers, and changes in sexual behavior. Furthermore, the authors assumed that there will be no increase in HPV induced cervical cancer if no intervention is implemented.

In this study the most cost-effective option would be to vaccine 15-year-old females targeting vaccine coverage of 30% ICER being 2,167 Euros per LYG.

Hungary: Dasbach et al. [53] studied the cost-effectiveness of adding the quadrivalent HPV6/11/16/18 vaccine in the current screening-based CC prevention strategy. The effects of and costs in preventing CC, CIN grades 2 and 3 (CIN2/3), CIN1 and genital warts in Hungary were estimated using a dynamic transmission model. The authors evaluated two strategies: vaccination of 12-year-old females and the same strategy with a catch-up program for females aged 12-24 years. The model has been established elsewhere [32] and for this study certain inputs were modified with Hungarian data (screening, treatment, mortality, and economic data) and the chosen vaccination strategies.

Vaccine coverage was assumed to be up to 85% and 10% for the catch-up program. The duration of protection was varied from 10 year to a lifetime. The costs for a 3-dose protocol were estimated at 279 Euros assuming no additional costs.

In this study both strategies would decrease HPV-induced diseases (CC, CIN2/3, CIN1) significantly (85-93% in 100 years) but with the catch-up program the results would emerge earlier. The ICERs for vaccinating 12-year-olds were 9,577/QALY and 10,646/QALY for the catch-up. According to the WHO criteria both the strategies could be estimated as cost-effective.

Brazil: Kim et al. [38] studied the cost-effectiveness of including males in a HPV vaccination program concluding that vaccinating females before sexual onset would be cost-effective and that it would be more cost-effective to increase vaccine coverage in females rather than include males in the program. Even though their results suggested that including males would result in health benefits for females the costs involved (a cost per-vaccinated individual of $50) were too high for this strategy to be as cost-effective as a female alone strategy. They linked a flexible dynamic open-cohort, age-structured (ages 0-90 in yearly intervals) compartmental model [29] to an empirically calibrated stochastic model of cervical cancer [44]. Strategies were evaluated using the incremental cost-effectiveness ratio. Reduction in life-time CC risk in a females-only strategy varied from 14% to 63% in a coverage range of 25% to 90%. Including males in the program decreased the risk another 4% in a coverage of 90% (for both sexes). Assuming coverage of 50% in both sexes the decrease in risk was 11%. In cost-effectiveness analyses including males into the program was in all scenarios less cost-effective (more costly and less effective) than aiming to increase the coverage in females.

The model does not include empirically validated age and gender specific HPV transmission data, vaccine efficacy data on males, the effect on HPV-6 and -11 associated genital warts or any other possible positive effects such as decrease in the number of other cancers associated with HPV. The authors point out that sexual behavior data is very limited, and it is likely that some of the females getting the vaccine will already have had the infection which will decrease the protective efficacy of the vaccine. There are also questions concerning bisexual or homosexual partnerships and independent CC risk factors that may be changing over time, such as smoking [96-98]. The vaccine uptake may be lower in rural areas and in regions where children are not in school. The authors also remind that empirical data concerning the duration of vaccine efficacy, magnitude of herd immunity, cross protection, interactions between HPV types and natural history of multiple infections is not yet available.

At $25 per-vaccinated individual (approximately $5 per dose), vaccinating pre-adolescent females alone was cost-saving compared to no vaccination in all considered coverage levels. At $50 or more vaccination was no longer cost-saving but still cost-effective the ICER being less than $200/YLS. The ICER for including males ranged from $810-18 650/YLS depending on coverage on females.

Mexico: Insinga et al. [67] used a dynamic transmission model to evaluate cost-effectiveness of HPV-vaccination while retaining current CC screening practices. The model has been described in detail earlier [32,99]. Dynamic models, such as this one, allow for estimating both the direct and indirect benefits of vaccination. The transmission of HPV infection is simulated by modeling sexual mixing thus including simulations reflecting real-life situations in which HPV is mainly sexually transmitted by both sexes. This is further reflected in the estimated benefits as the vaccine-induced herd-immunity effect is assumed to hinder HPV transmission in the population expanding the vaccine-induced benefits to unvaccinated population. In the case of the quadrivalent HPV6/11/16/18 vaccine the benefits include decreases in HPV-related cancers, their pre-states, and anogenital warts.

The authors modeled Mexican CC screening practice with local data and examined the modeled epidemiologic and economic output for 12-year-old female-only and both sex strategies with and without catch-up programs. They assumed vaccine coverage of up to 70%. Moreover, cross-protection was not included. A cost for the three doses was determined at about $240 U.S.

The productivity losses associated with HPV disease resulting from lost labor earnings due to morbidity or premature mortality, current population data were not available on the annual age-specific incidence of cervical cancer, CIN or genital warts, population data on the costs associated with all follow-up care for an incident episode of genital warts were not available. The incidence of HPV disease and costs of care may vary by healthcare provider and geographic region within Mexico.

As the most effective strategy they identified vaccination of 12-year-old females and males with a temporary catch-up program for 12-24-year-olds also for both sexes. The most cost-effective strategy had an ICER of 183,717 pesos/QALY (U.S. $16,702/QALY) when compared to 12-year-old vaccination of both sexes with a 12-24-year-old female catch-up program. At very high coverage levels for female vaccination the incremental cost-effectiveness of vaccinating males was less cost-effective.

Brazil: Vanni et al. [79] developed an individual-based dynamic model to capture herd-immunity effect and to model non-mutually exclusive events in their assessment of the cost-effectiveness of quadrivalent HPV vaccination for pre-adolescent female population in Brazil. The authors assumed that the vaccination would be added to current screening strategies. The authors also evaluated the cost-effectiveness of male vaccination concluding that it is not cost-effective.

Vanni et al. [79] note that their model differs from that of Goldie et al. [49] and Kim et al. [38] who have both evaluated the cost-effectiveness of HPV vaccine in Brazil. Vanni et al. [79] use a model which includes herd immunity effect and the screening strategies reflect the current practice in Brazil which is not the case in the study conducted by Goldie et al. [49] and Kim et al. [38] did include herd immunity effect in their model but they evaluated the cost-effectiveness of the bivalent vaccine, reported health benefits in YLS, and used a susceptible-infected-recovered algorithm (*vs.* susceptible-infected-susceptible algorithm used by Vanni et al. [79]).

The ICERs vary from 20 US$/QALY (cost saving) and 17 US$/YLS at 90% vaccine coverage with a cost of 25 US$ per individual. At lower coverage (50 and 70%) vaccination was cost saving. At higher costs per individual (55, 125, and 556 US$) the ICERs were still cost-effective (using GDP per capita as the threshold) ranging from 113 US$/QALY (cost saving) and 103 US$/YLS (cost per individual 55 US$, 50% coverage) to 5950 US$/QALY and 5414 US$/YLS (cost per individual 556 US$, 90% coverage). The authors, however, note that in the case of Brazil the proper threshold could be significantly lower (500 US$/YLS). All costs are aggregate costs in US dollars, index year 2008. The country-specific findings are summarized in Appendix 1 [100-102].

Finally, it should be noted that model uncertainties (Appendix 2) were considered very heterogeneously in the different model types, irrespectively whether they represented Markov models or Transmission dynamics models. In the latter, natural history of HPV infection and efficacy/effectiveness of HPV vaccination/vaccination strategies were often considered. In both model types data on risk factors, which may change over time, or the current epidemiological situation and predictions for the future disease burden were seldom present. Occupational health aspects were missing from most models. On the contrary, basic vaccine cost and screening assumptions, and some sensitivity analyses, were often included in both the model types [103-106].

Conclusion

The occurrence of CC in many upper-middle income group countries and low-income group countries are not remarkably different. It is, however, likely that urbanization and poor prospects for implementation of HPV mass vaccination and associated HPV-screening in the latter gives way to emerging hrHPV and CC epidemics in the future.

Both the Markov and the dynamic transmission models evaluated support implementation of HPV vaccination of girls in middle- and low-income countries with sustainable/reasonable vaccine prices. The sustainable vaccine prices, however, vary in a logarithmic scale between the upper middle-income and low-income countries.

The free impact on herd immunity from vaccinating both genders has not been properly evaluated in most cost-effectiveness studies ignoring the fact that HPV is the most sexually transmitted agent prone to be strongly influenced by herd immunity due to the assortative nature of sexual risk taking behavior. Also new modes of screening for the HPV vaccinated age-cohorts deserves further studies - the impact of vaccine coverage is pivotal in both.

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