

Minireview

Human papillomavirus vaccination in low-resource countries: lack of evidence to support vaccinating sexually active women

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Vaccines against the human papillomaviruses (HPV) that cause around 70% of cervical cancer cases worldwide are highly efficacious when administered before infection with the viruses, which occurs soon after initiation of sexual activity. Despite recommendations from key public health bodies that the primary target population for HPV vaccination should be young adolescent girls, numerous articles have suggested widening the target age group to include older adolescent girls and adult women. These articles cite evidence of efficacy and cost-effectiveness when making recommendations, and they rarely take into account the difficult resource-allocation issues faced by decision makers in low-income countries. Authors and sponsors of these articles are usually from high-income countries and sometimes include vaccine manufacturers. This review discusses the strengths and weaknesses of several types of evidence offered by these papers in support of vaccination of a broad age range of girls and women. It concludes that the greatest public health benefit and value for resources will come from vaccinating girls before sexual debut and exposure to HPV, particularly in low-resource areas.

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New technologies based on the discovery that cervical cancer is caused by oncogenic human papillomaviruses (HPV) have the potential to become the most effective tools for cervical cancer prevention in low-income countries. These countries shoulder the highest burden of this disease (Ferlay *et al*, 2010) and yet have almost no screening programmes – the key to the reductions in cervical cancer deaths in high-income countries over the past 40–50 years. The new technologies include HPV vaccines against the viral types responsible for at least 70% of cervical cancers and HPV screening tests that before long will be cheaper and easier to implement in developing countries than the Pap smears that revolutionised prevention in industrialised countries.

Two prophylactic vaccines have been approved by several regulatory authorities and are licensed in over 100 countries worldwide – a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and a bivalent vaccine against types 16 and 18. Randomised clinical trials demonstrated at least 93% efficacy against infections and precancerous cervical lesions caused by HPV types 16 and 18, the oncogenic types targeted by the vaccines, in young women with no evidence of current infection or previous exposure to these types (The FUTURE II Study Group, 2007; Paavonen *et al*, 2009). Human papillomavirus types 6 and 11 are responsible for most cases of genital warts. Analyses that included all women in the trials regardless of current or past HPV exposure resulted in significantly lower efficacy, on the order of 50% or less, suggesting that vaccinating before sexual debut will provide more value for resources used.

The pivotal trials of the two vaccines did not include girls younger than 15 years, but immuno-bridging studies showed that vaccinating girls aged 9–14 years resulted in antibody titres that were not inferior to those in the efficacy trials and were usually much higher (Pedersen *et al*, 2007). This finding, along with safety data, was essential for approvals and subsequent recommendations for girls as young as 9 or 10 to receive the vaccines. Based on the efficacy of the vaccines, the cost of vaccinations (including programme costs), the likelihood of achieving high coverage and the resulting cost-effectiveness for various groups, key public health bodies, including the World Health Organization (WHO), (World Health Organization, 2009) have recommended that highest priority be vaccinating girls before initiation of sexual activity.

Despite this global recommendation, numerous articles have suggested widening the target age group to include older girls and adult women, raising policy questions with regard to the best use of scarce resources. We conducted a critical review of the literature to weigh the strengths and weaknesses of evidence used to support recommendations for vaccinating beyond the age of sexual debut, and to propose likely benefits and drawbacks associated with various recommendations if applied in public health programmes in low-resource settings. The analysis is intended to aid policy-makers in developing countries that are deciding on populations to include for HPV vaccinations in their immunisation programmes.

METHODS

We performed a systematic PubMed search of English-language literature for original papers in the 5 years preceding July 2011, and for reviews in the 3 most recent years in major scientific

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journals, excluding those such as nursing and family practice publications. Search terms included combinations of the following: HPV vaccination, HPV infection, cost-effectiveness, efficacy, age, recommendations, and developing country. Subsequently we looked at papers cited in those found in the PubMed search. Papers on the epidemiology of HPV infection and on vaccine clinical trials were also reviewed. Articles with the major focus on the following topics were excluded: vaccinating males, acceptability, vaccine controversy, HIV-positive women, molecular biology, immune mechanisms, screening, genotype distribution, sexual behaviour, vaccination coverage, and cancers other than cervical cancer.

FINDINGS

Most papers that address the question of the appropriate age for HPV vaccination endorse the WHO recommendations for young adolescent girls as the primary target group, but many also advocate for vaccinating women after sexual debut, without differentiating between high- and low-resource settings. Recommendations for vaccinating after initiation of sexual activity generally are based on interpretations of two types of evidence: vaccine efficacy or cost-effectiveness. In Table 1, we present our overall conclusions from the literature assessed for this review. Vaccinating girls and women older than the primary target group could entail a 5- to 30-fold increase in the number of people to be vaccinated – depending on how many additional age groups were included – and an associated increase in burden on health personnel, cold chain, and other infrastructure, in addition to greater vaccine costs. However, catch-up efforts (up to approximately age 18) could be desirable in some low-resource countries where HPV vaccination may be lifesaving in adolescent girls whose future access to cervical screening is uncertain. Concerns that women might forego screening where it is available, because they believe vaccine is fully protective, become more important as women get older.

Our interpretation of the comparisons in Table 1 is that for resource-poor areas, drawbacks far outweigh benefits for vaccinating after sexual initiation. Why, then, do some authors still recommend vaccinating older girls and adult women? We analysed interpretations of vaccine efficacy – and the associated topic of the natural history of infection – and cost-effectiveness in the papers identified in our literature search.

Recommendations based on interpretations of vaccine efficacy

Of the 18 papers discussing the topics of vaccine efficacy and HPV infection, 5 gave unqualified support for vaccinating all ages; 5

expressed qualified support for a range of ages not exceeding 26 years; 1 indicated benefit for women up to 45 years; and 7 emphasised vaccinating before sexual debut. Only 3 papers discussed the situation in developing countries, with all recommending vaccination before sexual debut in these settings (Garland and Smith, 2010; Stanley, 2010; Elit *et al*, 2011) (see Table 2).

We noted four main arguments in this literature for vaccinating sexually active women; these are evaluated below. Our review provides counter-arguments to pro-vaccination arguments 1 and 2 and no support for argument 4, while recognising that argument 3 is still unsettled.

Argument number 1 Prevention of HPV infection, rather than cervical intraepithelial neoplasia grade 2 or worse (CIN2+) lesions, is equally acceptable as a vaccine efficacy endpoint for women older than age 26 years as it is for younger women.

Counter-argument number 1 The only data on the efficacy of HPV vaccine in women who are 27–45 years old derive from a randomised clinical trial of the quadrivalent vaccine (Castellsague *et al*, 2011) where the primary efficacy endpoint was the combined incidence of persistent infection, CIN, and external genital lesions related to HPV 6/11/16/18. Although the efficacy against the combined endpoint after 4 years of follow-up was statistically significant in both per-protocol-for-efficacy and intention-to-treat (ITT) populations, the CIN2+ outcomes in the ITT population, which more closely resembles older women who would be vaccinated in catch-up programmes, do not mirror the combined endpoint results (based primarily on infection) as they generally do among younger women in other trials. There were 21 cases of CIN2+ in the vaccine group and 27 in the placebo group (approximately 1% in each group) – a non-statistically significant difference.

The inadequacy of using HPV infection as the primary endpoint for efficacy in women over age 26 years is underscored by the refusal of the US Food and Drug Administration to grant approval for the quadrivalent vaccine for women aged 27–45 based on data from the above-mentioned trial of women up to age 45 years (Roberts, 2011).

Argument number 2 Some sexually active women will not yet have been infected by either, or at least not by both, of the oncogenic HPV types included in the vaccines (types 16 and 18), or in the case of the quadrivalent vaccine, may not have been infected

Table 1 Benefits and drawbacks associated with human papillomavirus (HPV) vaccination for different age groups in developing countries

	Older girls (14–18 years)	Young women (19–26 years)	Older women (27+ years)
<i>Benefits</i>			
Compared with vaccinating only girls aged 10–13 years	Slightly reduced but still significant efficacy, depending on the age of sexual debut Shorter time to discernible impact	Protection primarily for those with little or no sexual experience Protection against infection with vaccine HPV type not yet encountered ^a	Small number of women may be protected from late infection or re-infection
<i>Drawbacks</i>			
Compared with vaccinating only girls aged 10–13 years	Harder to reach (lower school attendance, may have left home) Greatly expanded cohort Reduced cost-effectiveness	Harder to reach (more scattered) and completion of three doses is less likely Greatly expanded cohort Substantially reduced cost-effectiveness	Very large and difficult to reach population to vaccinate Greatly reduced cost-effectiveness Very limited data on efficacy against disease endpoints Probable reduced risk of progression after age 45 years (hormonal changes) Greater delay in benefits compared with screening May reduce screening attendance ^b

Abbreviation: HPV = human papillomavirus. ^aType 16 is most likely to already be acquired, and type 18 and other oncogenic types (cross-protection) are less common, so limited benefit. ^bMay do so even for younger, sexually naïve vaccinees, but they will not be infected by the most common and virulent types when vaccinated (i.e., types 16 and 18) and will have a much smaller risk for cervical cancer.

Table 2 Reviews and commentaries on vaccinating various age groups based on efficacy interpretations

Country of first author	Potential conflict of interest ^a	Ages that will benefit	Source
India	Yes	Unlimited ^b	Basu <i>et al</i> , 2009
Belgium	Yes	Unlimited	Poppe <i>et al</i> , 2010
Spain	Yes	Unlimited	Castellsague <i>et al</i> , 2009
France	Yes	Not above 26	Monsonogo <i>et al</i> , 2010
Czech Republic	Yes	Before sexual debut	Prymula <i>et al</i> , 2009
United Kingdom	No	Unlimited	Adams <i>et al</i> , 2009
United States	No	Unlimited	Wright <i>et al</i> , 2008
United States	No	Not above 45	Lu <i>et al</i> , 2011
United States	No	Not above 26	Roberts, 2011
United States	No	Not above 26	Grant <i>et al</i> , 2011
United States	No	Little benefit above 18	Castle <i>et al</i> , 2009
Finland	No	Little benefit above 18	Paavonen, 2010
United Kingdom ^c	No	Before sexual debut	Stanley, 2010
Australia	No	Before sexual debut	Garland and Smith, 2010
Canada	No	Before sexual debut	Elit <i>et al</i> , 2011
United States	No	Before sexual debut	Hildesheim and Herrero, 2007
United States	No	Before sexual debut	Solomon <i>et al</i> , 2009
United States	No	Before sexual debut	Markowitz <i>et al</i> , 2009

^aYes: ≥ 1 author from vaccine manufacturer or writing funded by company. No: no support or authorship from vaccine companies. However, authors may have participated in clinical trials funded by vaccine companies, received honoraria, or may be company consultants. ^bUnlimited: no age is given over which vaccination is not recommended. Papers may not specifically state that all ages should be vaccinated but usually refer to 'all sexually active women.' ^cPaper supports vaccinating before sexual debut in developing countries but also states that older women in high-resource countries may benefit if they choose to be vaccinated.

by HPV types 6 or 11, which cause most genital warts (Wright *et al*, 2008; Adams *et al*, 2009; Basu *et al*, 2009).

Counter-argument number 2 Young sexually active women are less likely than somewhat older women to have been infected with both oncogenic vaccine virus types, but the incidence of new infections increases rapidly with age up to around age 25 years, at least in most high- and intermediate-resource areas investigated, and then declines (Franceschi *et al*, 2006). As the vaccines have no effect on current infections (Hildesheim and Herrero, 2007), vaccinating sexually active women runs the risk of having little benefit among these women who are young and more likely to have active infections.

In the one reported trial on vaccine efficacy in older women (Castellsague *et al*, 2011), the very low rates of CIN2+ or external genital lesions in HPV-naïve women in the placebo group suggest that whether older women have been infected with all vaccine types or not, they are at very low risk of incident disease at this time in their lives.

To translate recommendations for vaccinating before sexual debut into plans for vaccinating at or before a specific age, decision makers require information on the age of sexual debut in their countries or areas. Reports on sexual practices in the world indicate that very early intercourse might be occurring in adolescence, with median age of sexual debut in the mid-teens in many countries (e.g., Singh *et al*, 2000). This means that 50% of young women initiated sexual activity before these ages; thus, vaccination programmes aiming to protect the maximum number of young adolescents must plan to vaccinate well before the mid-teens.

Argument number 3 Natural immunity cannot protect against re-infection by the same HPV type, but vaccination can.

Counter-argument number 3 Conclusive evidence on whether natural immunity is protective is not yet available. Indirect evidence of possible natural immunity comes from an analysis of the subpopulation of seropositive women (those with evidence of previous HPV infection) in a large clinical trial of the bivalent vaccine (Szarewski *et al*, 2011). Although the authors highlighted vaccine efficacy in women seropositive and DNA negative, the confidence intervals for significance at the 5% level included zero (not significant) for one analysis, and were very wide in another. An interesting result not called out by the authors was the finding that among women in the placebo group, those who were seropositive and DNA negative had about half the rate of CIN2+ as those who were seronegative and DNA negative, a hint that natural immunity might be providing protection.

Evidence is also lacking on whether HPV vaccines protect against re-infection by or re-activation of vaccine viral types. In a sub-analysis of women who were seropositive and DNA negative in three clinical trials of the quadrivalent vaccine (Olsson *et al*, 2009), there were no cases of CIN in the vaccine groups, but seven in the placebo groups. However, statistical significance for vaccine efficacy was only reached when including cases of CIN1, which is currently considered a mere marker of HPV infection. Efficacy against CIN2+ was not shown.

Argument number 4 Older women have high risk for new infections, and those who develop a new infection are at high risk for progression (Basu *et al*, 2009; Poppe *et al*, 2010).

Counter-argument number 4 In a report from a study of more than 8000 women in Costa Rica, regardless of the woman's age, newly detected infections were associated with very low absolute risk of persistence or CIN2+ (Rodriguez *et al*, 2010). On the other hand, prevalent infections in older women, especially in inadequately screened populations, are much more likely to be persistent infections (acquired years earlier) than those in younger women, and the vaccines have no effect on persistent infections (Hildesheim and Herrero, 2007), making it clear that any comparison of CIN2+ risk across women of different ages should separate incident from persistent infections.

A recent report offers indirect evidence that older women may actually be at lower risk of disease due to new HPV infection. This re-analysis that pooled data from 20 studies on cervical cancer found that the risk of cervical cancer increases as the square of time since first intercourse, using first intercourse as a reasonable proxy for first exposure to HPV (Plummer *et al*, 2011). According to this report, the relationship between HPV infection and cervical cancer resembles that found for other cancers caused by strong early-stage carcinogens (e.g., tobacco smoking and lung cancer), with incidence rates proportional to a power of the duration of exposure to the relevant carcinogenic agent and with a delay between infection and cancer. The multi-stage cancer model postulates that a certain number of cellular changes must occur for malignant transformation, which explains the delay and predicts that new HPV infections acquired later in life are less likely than those incurred earlier to develop into cervical cancer. In addition, epidemiological and animal data suggest that, although HPV is the cause of cervical cancer, steroid sex hormones are the fuel of HPV-driven carcinogenesis in the cervix. In populations where screening has not distorted the age distribution of the disease, cervical cancer shows a flattening in age-specific incidence rates at the time menopausal changes start (Plummer *et al*, 2011). Thus, vaccinating women at this time may have little benefit because the falling levels of steroid sex hormones appear to diminish the potential for malignant transformation of new HPV infections.

Authorship of papers with age recommendations for HPV vaccinations based on efficacy

In analysing the 18 papers on the efficacy of HPV vaccines as well as the literature on HPV infection, we noted that most are written by investigators in high-resource countries, where governments can afford to implement vaccination programmes and private individuals may wish to pay for vaccination even if the benefit is minimal. Some were funded by vaccine manufacturers or co-authored by company employees (Table 2). Of the 18 papers, 5 had such potential conflicts of interest, and 3 of these recommended vaccinating unlimited ages. All except 1 (Basu *et al*, 2009) of the 18 articles were authored by investigators in high-income countries.

Recommendations based on interpretation of cost-effectiveness

Cost-effectiveness studies use mathematical models that combine disease and natural history parameters, vaccine-efficacy findings, and estimated vaccine and health system delivery costs to compute the extra quantity and quality of life provided by an intervention. The intervention is usually considered cost-effective if the cost per quality-adjusted life year (QALY) is less than or equal to the gross domestic product per capita of a given country.

Many cost-effectiveness analyses have modelled HPV vaccination for young adolescent girls, usually 12 years of age, and have found that vaccination at this age is cost-effective in high-income countries, and a 2008 study on cost-effectiveness of vaccinating girls before the age of 12 years in 72 developing countries concluded that vaccination could be cost-effective if the price of vaccine per dose was US\$2 (Goldie *et al*, 2008). Our search identified 13 papers that evaluated vaccinating beyond age 12 years, all modelling cost-effectiveness in high- or middle-income countries (see Table 3). Six of these found vaccination cost-effective up to ages 24–26 years, the maximum ages studied, and one that modelled to age 50 years found that vaccinating to age 25 years, but not beyond, was cost-effective. Three found that vaccinating up to ages 15, 18, or 21 could be cost-effective. Another paper, which considered women up to 35 years of age in several countries, found vaccination most cost-effective up to 15–19 years, depending on the age for the peak of HPV infection in the region under question. Two papers reported that only vaccinating girls ≤ 12 years old was cost-effective. Thus, in the few studies that have modelled beyond age 26, none has found including older ages to be cost-effective.

As the papers we reviewed are mathematical modelling studies, the reasons for disparate results must be found in study assumptions. Factors that can change the results of studies include:

- Basic model structure: static (e.g., Markov) or dynamic (e.g., population- or individual-based)
- Duration of vaccine protection
- Natural infection rates in population
- Degree of natural immunity after infection
- Definition of 'cost-effective'
- Price estimated for vaccine
- Inclusion and estimate of administrative costs
- Effect and cost of screening
- Health outcomes included (e.g., warts, male outcomes for quadrivalent vaccine, other HPV-related cancers)
- Impact on quality of life for cervical lesions, genital warts

Estimates of cost per QALY can increase dramatically when using less favourable assumptions for these factors; for example, reduced duration of vaccine protection, reduced vaccine efficacy, fewer health outcomes, or reduced impact of health outcomes on quality of life. Virtually all studies on the quadrivalent vaccine include outcomes on genital warts and this typically lowers the cost per QALY.

In a modelling study of mid-adult women in the United States, researchers found that HPV vaccination provided only nominal benefits in the context of current screening recommendations and practice among women aged 35–45 years (Kim *et al*, 2009). A review of cost-effectiveness studies included a report that less than about 5% of the total health benefits of vaccinating 12- to 44-year-olds were attributable to vaccination of women after their mid-twenties (Grant *et al*, 2011).

Authorship of papers with age recommendations for HPV vaccinations based on cost-effectiveness

All 13 of the papers that met our search criteria for cost-effectiveness presented analyses for middle- or high-income countries. Eight of the studies were funded by a vaccine manufacturer or had at least two authors who were employees of a vaccine company (Table 3). Of these, seven found vaccinating to ages 24–26 years to be cost-effective. The other paper reported that depending on the region, HPV vaccination could be cost-effective to age 15, 17, or 19 (Suarez *et al*, 2008). On the other hand, in the

Table 3 Cost-effectiveness studies of HPV vaccination in sexually active women

Country studied	Potential conflict of interest ^b	Analysed ages to	Cost of vaccination ^c	Cost-effective for ages ^a			Source
				14–18	19–26	27+	
United Kingdom	Yes	24	\$346	CE	to 24	NA	Dasbach <i>et al</i> , 2008a
Norway	Yes	24	\$468	CE	to 24	NA	Dasbach <i>et al</i> , 2008b
United States	Yes	24	\$360	CE	to 24	NA	Elbasha <i>et al</i> , 2007
United States	Yes	24	\$360	CE	to 24	NA	Elbasha <i>et al</i> , 2009
Mexico	Yes	24	\$240	CE	to 24	NA	Insinga <i>et al</i> , 2007
Australia	Yes	26	\$320 ^d	CE	CE	NA	Kulasingam <i>et al</i> , 2007
Netherlands	Yes	50	\$384	CE	to 25	Not CE	Westra <i>et al</i> , 2011
Chile, Finland, Ireland, Poland, Taiwan ^e	Yes	35	\$210–\$549	CE	Not CE	Not CE	Suarez <i>et al</i> , 2008
United States	No	34	\$500	CE	to 21	Not CE	Chesson, 2010
United Kingdom	No	25	\$279 ^d	CE	Not CE	NA	Jit <i>et al</i> , 2008
Ireland	No	26	\$402	to 15	Not CE	NA	Usher <i>et al</i> , 2008
United States	No	26	\$360	Not CE	Not CE	NA	Kim and Goldie, 2008
United States	No	30–45	\$387	Not CE	Not CE	Not CE	Kim <i>et al</i> , 2009

Abbreviations: CE = cost-effective; NA = not available. ^aAnalyses generally consider vaccinating girls before sexual debut (≤ 12 years) to be cost-effective. ^bYes: ≥ 2 authors from vaccine manufacturer, article funded by company, or assisted by commercial writing/analysis company funded by vaccine manufacturer. No: academic or clinical authors, NGO or government funding. ^cFor the 3-dose course. All converted to current US\$. For all except the paper on the five countries, cost includes administration costs. ^dFor school-based programme; US\$434 if administered by physician. ^eThese countries were all reported in the same study; different ages for starting vaccination (15, 17, or 19) were found to be the most cost-effective, because of the time of the peak HPV prevalence in the countries. Vaccine cost does not include administrative costs.

group of papers not directly funded by vaccine manufacturers or authored by employees, the highest age for which vaccinating was found to be cost-effective was 21 (one study), and two studies found that only vaccinating 12-year-old girls was cost-effective.

DISCUSSION

WHO guidance

The WHO position paper on HPV vaccines states that as HPV vaccines are prophylactic, the largest impact of vaccination is expected from high coverage of young adolescent girls before first sexual activity and exposure to the viruses, and recommends that females aged 9 or 10 through 13 be the primary target population (World Health Organization, 2009). With this clear guidance, it is puzzling that many authors continue to recommend vaccinating older girls and adult women without acknowledging the implications for resources in low- and middle-income countries. Although some young women will benefit from vaccination after sexual initiation because they have not yet been infected with all vaccine HPV types, it is much more efficient and cost-effective to vaccinate earlier.

Efficacy

Vaccine efficacy against CIN2+ caused by HPV16/18 in the pivotal clinical trials for both the quadrivalent (The FUTURE II Study Group, 2007) and bivalent (Paavonen *et al*, 2009) vaccines was around 50% in women aged 15–26 years and 22.4% in older women (Castellsague *et al*, 2011) when total trial populations were analysed. But even these mixed, ITT populations do not approximate a 'real world' setting, because stringent trial inclusion criteria will not apply in public immunisation programmes.

Cost-effectiveness

For high-income countries with well-managed cervical cancer screening programmes, offering HPV vaccinations to sexually active women in some age groups (Jit *et al*, 2008; Usher *et al*, 2008) may lead to savings in screening programmes and may shorten the time by which a lower incidence of precancerous lesions and, eventually, a lower rate of cervical cancer are seen. Although these are the very places where screening programmes provide excellent protection against cervical cancer, such countries may be able to afford the additional benefits of vaccinating young women.

In developing countries, where screening services are not available or have only been introduced in a few areas, one might argue that vaccinations among older adolescents and young women could speed up the rate at which cervical cancer incidence and deaths decline while screening programmes get underway. However, in these countries, the notion of cost-effectiveness does not always correspond to affordability or to best use of resources compared with other cost-effective interventions; factors such as

population health needs and local priorities must also be considered.

The economic challenges of increasing vaccine purchases and the logistical difficulty of achieving high coverage among older girls and young women in developing countries raise serious concerns (World Health Organization, 2009). Recently the manufacturer of the quadrivalent vaccine announced that it will be available to the GAVI Alliance (GAVI) at a price of US\$5 per dose, and the GAVI Board announced that it would take the first steps towards supporting the introduction of HPV vaccines in developing countries (GAVI Alliance, 2011). If GAVI is able to subsidise the vaccine cost for eligible low-income countries, vaccinations should become affordable even in very low-income settings for girls around the age of 12 years.

Feasibility of reaching different age groups with vaccine and alternatives

Vaccinating children beyond the ages for infant immunisations (the target population for HPV vaccination) in these regions is a challenge, but reaching girls of primary school ages is a credible strategy. As a result of Goals 2 and 3 of the Millennium Development Goals, girls' attendance in primary school has climbed dramatically in all regions of the world making school-based delivery one of the most promising systems for achieving high coverage with the HPV vaccines in low-income countries.

In a broad range of socioeconomic settings, modelling has demonstrated that screening, with treatment when necessary, is a very practical and cost-effective approach for cervical cancer prevention for sexually active women even if performed only once, around age 35 years. In principle, Pap smear (where already in place and functioning well), HPV DNA screening tests, or less costly methods such as visual inspection may be worthwhile in low-resource areas.

Conclusions

While individual women may benefit from HPV vaccination after initiating sexual activity, the number not exposed to vaccine HPV types decreases steadily with time after sexual debut. The greatest public health benefit and value for resources will come from vaccinating girls before sexual debut and exposure to HPV, particularly in low-resource areas. Most papers that are favourable to vaccinating a broad age range of sexually active women are authored by investigators in high-income countries or are funded by vaccine manufacturers. These papers rely on very weak evidence of vaccine efficacy among women aged 27 years or older and they do not take into account the difficult resource-allocation issues faced by decision makers in low-income countries. Before broadening the WHO-recommended age range for public HPV vaccination programmes in their regions, policymakers should make sure that the vaccination is firmly in place for young adolescent girls who can benefit the most from it and concentrate on screening-based approaches for cervical cancer prevention among older women.

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