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Human papillomavirus (HPV) vaccination: from clinical studies to immunization programs

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ABSTRACT

Cervical cancer incidence and mortality have decreased in high-income countries, but low- and middle-income countries continue to bear a significant burden from the disease. Human papillomavirus (HPV) vaccines are a promising alternative for disease control; however, their introduction is slow in settings with greater need. We conducted a review of HPV vaccine efficacy and effectiveness reported in clinical trials and population-based studies. Efficacy of HPV vaccines is close to 100% when using a three-dose schedule in HPV-negative young women (<25 years old) for protection against persistent infection and HPV vaccine-type associated pre-cancerous lesions. Furthermore, sustained protection for up to 12 years of follow-up has been demonstrated; cross-protection against non-vaccine types is particularly observed for the bivalent vaccine, and preliminary data regarding impact on invasive cancer have emerged. Given its lower efficacy, catch-up vaccination beyond 19 years of age and proposals for vaccinating adult women deserve careful evaluation in accurately designed studies and economic analyses. Despite positive results regarding immunogenicity and post-hoc analysis for cervical intra-epithelial neoplasia in clinical trials, population-based data for prime and booster two-dose schedules are not available. Evaluation of vaccine safety from surveillance systems in immunization programs that have already distributed more than 270 million doses found no association of HPV vaccination with serious side effects. The introduction of HPV vaccination in national immunization programs remains the main challenge in tackling the burden of cervical cancer (up to 2018, only 89 countries have introduced vaccination worldwide, and most of these are high-income countries). Access models and technical capacity require further development to help low- and middle-income countries to increase the pace of vaccine delivery. Alternative approaches such as one-dose schedules and vaccination at younger ages may help reduce the programmatic and economic challenges to adolescent vaccination.

INTRODUCTION

Several high- and middle-income countries have noted a significant reduction in cervical cancer incidence and mortality after the introduction of cytology-based screening[1]; however, low- and middle-income countries continue to bear a significant burden of disease, accounting for approximately 87.5% of new cases and 91.2% of cervical cancer deaths.[2] Moreover, socially disadvantaged women face the highest mortality rates in all settings.[3] Although cervical cytology is available in most countries around the world, organizing screening throughout the women's lifespan is challenging and resource demanding, thereby making cytology-based screening unsustainable in most low- and middle-income countries.[4] The identification of persistent high-risk human papillomavirus (HPV) infection as a necessary cause of cervical cancer prompted technology development around new preventive tools and strategies for disease control.[5–7]

HPV vaccines have shown high efficacy in the prevention of cervical intra-epithelial neoplasia (CIN) associated with vaccine types,[8] thus providing a promising alternative for reducing the burden of disease in low- and middle-income countries, reducing social inequalities in cervical cancer control, and improving women's health. The implementation of HPV immunization programs, however, is low; this is particularly observed in low- and middle-income countries where they are needed most (approximately 70% of invasive cervical cancer occurs in countries that have not introduced HPV vaccines),[9] and such implementation faces economic, operational, cultural, and political constraints. Despite the significant amount of high-quality evidence, HPV vaccination has been associated with significant controversy inside and outside the scientific community regarding its efficacy, safety, and cost-effectiveness.[10 11]

Several reviews condense data from clinical studies on these topics and some have included post-licensure data on vaccine safety.[12] Moreover, after the introduction of HPV vaccines in national immunization programs, results from population-based studies on short-term outcomes have become available suggesting vaccine effectiveness on prevention of HPV infection, genital warts, pre-cancerous lesions, and most recently HPV-associated cancers. This review summarizes information regarding the current status of HPV vaccination with special focus on population-based information as a source of public health evidence of both vaccine effectiveness and safety.

HPV VACCINES EFFICACY

Three HPV prophylactic vaccines are currently available in the market (Table 1). All vaccines prevent HPV 16 and 18 infections as the most common high-risk HPV types in cervical cancer among all populations,

Table 1 Characteristics of available HPV vaccines

Manufacturer and trade mark name	Merck & Co Gardasil	Merck & Co Gardasil 9	Glaxo Smith Kline Cervarix
HPV types	16,18,6,11	16,18,6,11,31,33,45,52,58	16,18
Indication	Girls and women 9 through 26 years old	Girls and women 9 through 45 years old	Girls and women 9 years old and above
	Boys and men 9 through 26 years old	Boys and men 9 through 45 years old	
Vaccination schedules	0-2-6 months	0-2-6 months	0-1-6 months
	0 and 6–12 months*	0 and 6–12 months*	0 and 5–13 months*
Recombinant technology	Purified L1 VLP from *Saccharomyces cerevisiae*	Purified L1 VLP from *Saccharomyces cerevisiae*	Purified L1 VLP from Baculovirus expression system in *Trichoplusia ni* cells
Adjuvant	Amorphous aluminum hydroxyphosphate sulfate	Amorphous aluminum hydroxyphosphate sulfate	AS04 adjuvant system: aluminum hydroxide ($Al(OH)_3$) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL).

Sources: Gardasil: https://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf. Gardasil 9: https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf. Cervarix: https://au.gsk.com/media/265103/cervarix_pi_011_approved.pdf.
Brand names may be different between countries.
*Alternative two-dose schedule for girls 9 to 14 years old.
HPV, human papillomavirus.

accounting for 70% of cases worldwide.[13] The quadrivalent vaccine (Gardasil) protects against low-risk HPV types 6 and 11 associated with genital warts and respiratory papillomatosis; and the nine-valent (Gardasil 9) protects against five additional high-risk HPV types (31, 33, 45, 52, and 58) responsible for an additional 18.7% of cervical cancer cases worldwide.[13]

The efficacy of HPV vaccines for cervical cancer prevention has been extensively assessed from clinical trials utilizing CIN grade 2 or higher lesions (CIN2+) and 6 months persistent high-risk HPV infection as surrogate endpoints in women 16 years and older; furthermore, immunobridging studies for girls under 16 years old have been conducted as recommended by the World Health Organization-International Agency for Research on Cancer (WHO-IARC) working group.[14] The overall risk reduction of quadrivalent and bivalent vaccines in HPV-negative women at baseline (naïve population) for 6 months persistent infections is 94% with the standard three-dose schedule (Table 2). Specific reports for each vaccine show 96% and 94% efficacy, respectively, as per protocol analyses (Table 2). Overall protection against HPV16/18 associated CIN2+ in naïve populations is estimated to be 93% among women aged 15 to 26 years old and 84% for women aged 24 to 45years old (Table 2). For both quadrivalent and bivalent vaccines, specific reports reveal 98% efficacy against HPV16/18 associated CIN2+ lesions (Table 2).

Immunogenicity of alternative vaccine schedules for the quadrivalent and bivalent vaccines show no inferiority in two versus three doses in girls (<15 years old), higher antibody titers for two doses in girls (<15 years old) compared with three doses in women (15–25 years old), and higher antibody titers for longer intervals between doses. This suggests that prime and booster doses (0 and 6–12 months) are more immunogenic than prime to prime doses (0 and 2 months).[15] Clinical outcomes have not been directly evaluated in clinical trials with a randomized comparison of alternative vaccine schedules. One suspended trial found no difference in 6 months persistent HPV 16/18 infections between one, two or three doses of the quadrivalent vaccine[16]; however, indirect data from a non-randomized analysis comparing vaccinated and non-vaccinated girls observed 69% overall risk reduction for one or two doses (Table 2). However, indirect evaluations of CIN2+ and CIN3+ outcomes indicate no difference between three or fewer doses (Table 2).

Antibody titers in vaccinated girls are significantly high and sustained over a period of 8 to 10 years for the quadrivalent and bivalent vaccines.[17] A 10-year observation for the bivalent vaccine revealed significantly lower antibody titers for both HPV 16 and 18 in women 26–45 and 46–55 years old compared with women 16–25 years old; however, for all age groups, antibody titers against both HPV types are significantly higher than those induced by natural infection.[18] Protection against 6 months persistent HPV16/18 infection has been demonstrated for the bivalent and quadrivalent vaccines for observation periods over 5 years (Table 2), although protection against CIN2+ lesions has not reached statistical significance in long-term analyses in clinical trials due to the low number of cases available for study.[19]

The nine-valent vaccine shows a 96% efficacy against 6 months persistent infection of HPV types 31, 33, 45, and 52, and 58% and 96.3% against associated CIN2+ and adenocarcinoma in situ (Table 2). The observed risk reduction of CIN2+ lesions with the nine-valent vaccine irrespective of HPV type is 33.8% compared with the quadrivalent vaccine; however, the difference does not gain statistical significance due to the low number of cases.[20] Although no direct comparison for clinical outcomes is currently available, the quadrivalent and bivalent vaccines have shown cross-protection against non-vaccine HPV types (Table 2). Higher seropositivity for HPV 31 and 45 with the bivalent vaccine have been observed (HPV31 61% and 86%, HPV45 16% and 50%) whereas no difference is observed for HPV types 33, 52, and 58. Despite the inclusion of non-naïve women in the analysis, a positive correlation between

Table 2 Efficacy of HPV vaccines in clinical studies

Vaccine type	6 months persistent infection	CIN2+	CIN3+	AIS	Genital warts
A. Protection against HPV16/18 and associated lesions					
Vaccination of women younger than 25 years, three-dose schedule					
Overall[A1]	94% (91 to 95)	93% (85 to 97)	93% (71 to 98)	88% (36 to 99)	
Bivalent vaccine	94% (92 to 96)[A2]	98% (88 to 100)[A2]	92% (67 to 99)[A3]	100% (9 to 100)[A3]	
Quadrivalent vaccine	96% (83 to 100)[A2]	98% (94 to 100)[A2]	97% (88 to 100)*[A3]	100% (31 to 100)*[A3]	96% (91 to 99)*[A3]
Schedules with fewer than three doses†					
Overall[A1]		90% (74 to 96)	94% (76 to 99)		
Bivalent vaccine[A1]	88% (58 to 97)	93% (77 to 100)	96% (26 to 100)		
Quadrivalent vaccine		96% (26 to 100)*[A1]	94% (53 to 99)[A1]	85% (–197 to 99)[A1]	71%(79 to 96)‡[A4]
Vaccination of women older than 25 years, three-dose schedule					
Overall[A1]	89% (80 to 94)	84% (26 to 96)			
Bivalent vaccine	91% (79 to 97)[A2]	84% (–36 to 98)[A1]			
Quadrivalent vaccine	85% (68 to 94)[A2]	83% (–37 to 98)[A1]			
Schedules with fewer than three doses†					
Overall[A1]	69% (46 to 82)	39% (–167 to 86)			
Bivalent vaccine	84% (36 to 98)§ [A4]	67% (–215 to 97)[A1]			
Quadrivalent vaccine[A1]	69% (39 to 84)	3% (–580 to 86)*			
Duration of protection over 5 years for vaccination of women 16–25 years old					
Overall[A6]	95% (84 to 99)				
Bivalent vaccine[A9]	100% (84 to 100)	100% (–123 to 100)			
Quadrivalent vaccine[A8]		100% (84 to 100)	100%		
B. Protection against HPV other than 16/18 and associated lesions for vaccination of women 16–25 years old					
Bivalent vaccine¶	HPV31 77% (69 to 83) HPV33 45% (25 to 60) HPV45 74% (58 to 84) HPV52 20% (–8 to 40) HPV58 3% (–48 to 36)[A2 A3]	Irrespective of HPV type 62% (47 to 73)[A2]	Irrespective of HPV type 93% (79 to 99)[A2]	Irrespective of HPV type 100% (31 to 100)[A2]	
Quadrivalent vaccine¶	HPV31, 33, 45, 52, 58 18% (5 to 29)[A2]	Irrespective of HPV type 22% (3 to 38)[A2]	Irrespective of HPV type 43% (24 to 57)[A2]	Irrespective of HPV type 100% (<1 to 100)[A3]	Irrespective of HPV type 83% (74 to 89)[A3]

Continued

Table 2 Continued

Vaccine type	6 months persistent infection	CIN2+	CIN3+	AIS	Genital warts
Nine-valent vaccine**	HPV31, 33, 45, 52, 58 96% (95 to 97)[A5]	HPV31, 33, 45, 52, 58 97% (82 to 100)†† Irrespective of HPV type 34% (22 to 45)†††‡‡[A5 A7]	HPV31, 33, 45, 52, 58 100% (39 to 100)††[A5]		Irrespective of HPV type 100% (−12 to 100)[A5]

Overall: report combining bivalent and quadrivalent vaccines. Protection irrespective of HPV type comprises outcomes associated with any HPV type. Data in parenthesis correspond to 95% CIs. For presentation purposes all decimal numbers are rounded up
References A1 to A7 are available in the online supplemental material
*Includes HPV 6 and 11.
†Based on post hoc analyses.
‡Based on incidence rate ratios.
§Report for a two-dose schedule.
¶Cross-protection against non-vaccine types.
**Additional risk reduction compared with the quadrivalent vaccine.
††Includes AIS.
‡‡Estimates by authors based on Pink *et al*.[23]
AIS, adenocarcinoma in situ; CIN, cervical intra-epithelial neoplasia; HPV, human papillomavirus.

seroconversion and protection against 6 months persistent infections was found in a recent review.[21] In naïve cohorts, the overall risk reduction of CIN2+ lesions irrespective of the HPV type is 58% (bivalent 65%, quadrivalent 43%), and overall risk reduction for CIN3+ is 78% (bivalent 93%, quadrivalent 43%) (Table 2).[22]

Economic Evaluations

Several economic models have been used to inform decision makers on the introduction of HPV vaccines in immunization programs in lower- and middle-income countries; however, a high heterogeneity is observed between the models regarding input parameters, model assumptions, clinical outcomes, and quality of data.[23 24] Furthermore, the type of economic evaluation (cost-utility or cost-effectiveness), type of model (dynamic, static, hybrid) and cost perspective (payer, society) are also variable.[23]

Most economic evaluations from different settings find HPV vaccination of pre-adolescent girls to be cost-effective; furthermore, cost-effectiveness ratios for these programs are determined to be better than those for programs including additional age-cohorts or boys and in which vaccine price is the strongest cost-effectiveness determinant.[25] The economic evaluation of male vaccination is also highly sensitive to the spectrum of HPV-associated disease included in the model, and catch-up vaccination is significantly dependent on the age of vaccination with a greater decrease in cost-effectiveness for vaccination after 18 years old.[26 27]

Analyses from low- and middle-income countries face several challenges given the low availability, quality, and accessibility of data; thus, major assumptions have to be made including cost per vaccinated girl, vaccine coverage and screening coverage, and follow-up.[28] HPV vaccination in pre-adolescent girls requires a different delivery system than regular vaccines for children; hence, cost per vaccinated girl might be higher, and adaptation of delivery costs from similar countries where HPV vaccines have already been introduced is recommended as an option to improve cost-effectiveness studies in low- and middle-income countries.[28] Similarly, costs and performance of cervical cancer screening deserves more accurate estimates since the organization of call-recall systems during women's lifespan and follow-up of women throughout the clinical pathway (screening, diagnosis, treatment) requires a significant investment in program organization, and adaptation of costs from similar countries in the region could be an option.

Economic evaluations from high-income countries in North America, Europe and Oceania have shown the nine-valent universal or female HPV vaccination to be cost-effective or cost-saving compared with the quadrivalent HPV vaccination within the price range explored (an additional US$23 to US$47 and less than US$13 for cost-effectiveness and cost-saving observations, respectively).[29–33] Although some analyses from African countries have been published for the nine-valent vaccine, the limitations previously described for economic evaluations in low- and middle-income countries suggest that there is still a need for improving the quality of data to obtain robust estimations.

HPV Immunization Programs

In 2018, 89 countries had introduced HPV vaccination in national immunization programs according to WHO registries: 13 in Africa, 27 in the Americas region, 33 in Europe, eight in Asia, and eight in Oceania (Figure 1). These data correspond to approximately 55%

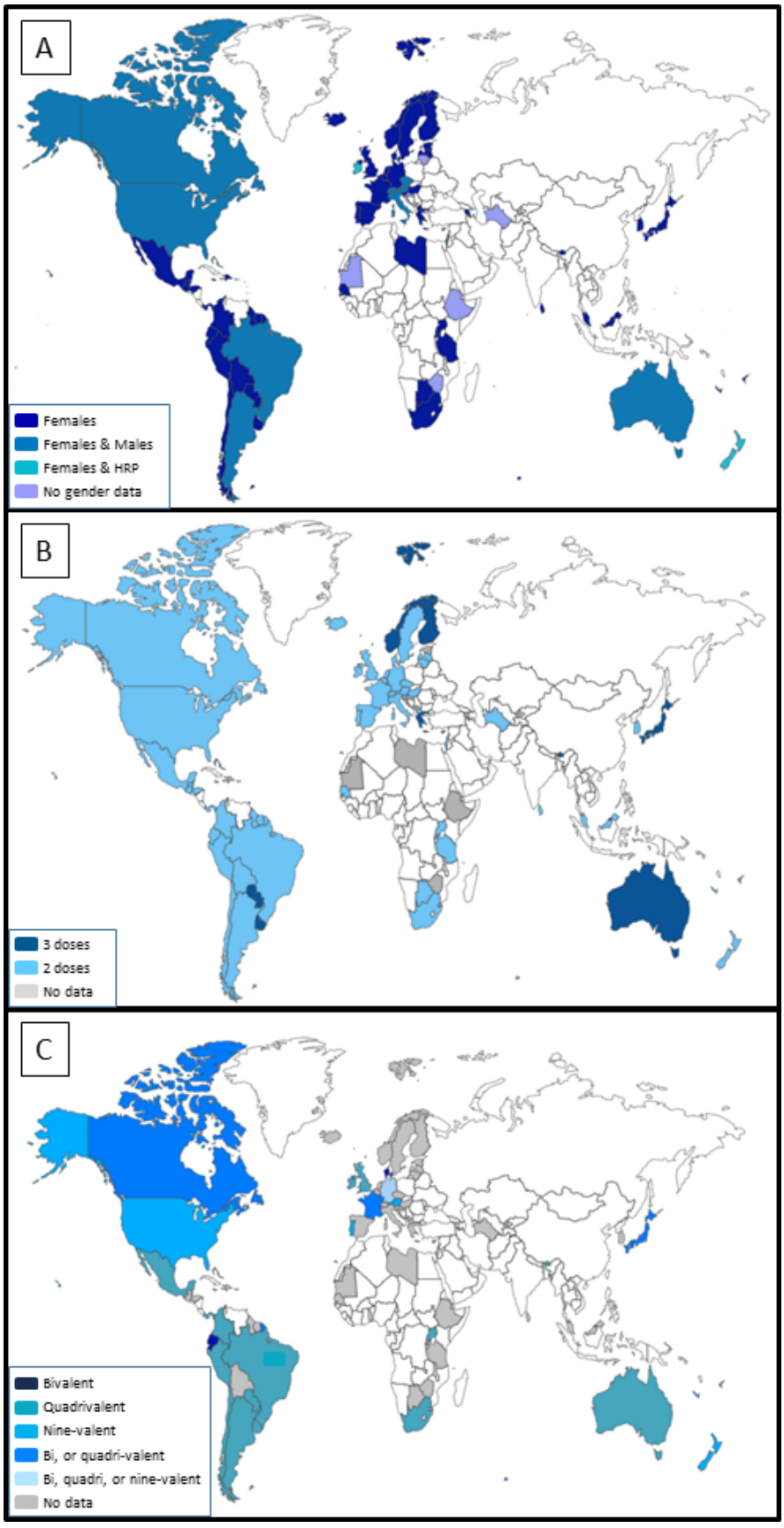

Figure 1 Human papillomavirus (HPV) vaccination in national immunization programs. (A) Countries with HPV vaccination in national immunization programs. (B) Vaccine schedules according to number of doses. (C) Vaccine type in national immunization programs. HRP, high-risk populations might comprise men who have sex with men, HIV positive patients, and transplanted patients. Data up to December 2018. Sources.[35 37 65–68]

of high-income countries and 14% of low- and middle-income countries.[34] For most countries, girls aged 9–14 years old are the primary target group with varying catch-up vaccinations available for individuals up to 26 years old[35]; only a few countries are vaccinating boys or special high-risk populations (Figure 1).

Although all countries use combined strategies to deliver HPV vaccination to the primary target groups, the main strategy for vaccine delivery is school vaccination. In 2017, 40 out of 82 countries reported vaccination in schools, 23 countries reported vaccination in health centers, and 11 countries mixed methods as the basic strategy for HPV vaccine delivery.[36] Our investigations did not yield any worldwide compiled information on HPV national vaccination coverage from governmental agencies. For the year 2014, coverage was estimated for 64 countries with HPV vaccination available under their national immunization program[37]; the data showed that 33.6% of women who were 10–20 years old received the full course of vaccines in high-income countries, whereas only 2.7% received it in less developed regions. By continent, the lowest coverage for girls aged 10–14 years (main target group) was observed in Asia (0.5%) and Africa (1.7%)—the two continents bearing the highest burden of cervical cancer mortality (Figure 2A). By world region, Northern Europe, Australia and New Zealand, and South America reported the highest coverage within this age group (46.2%, 41.5%, and 40.4%, respectively). Some additional analyses, including pilot experiences, revealed 20% higher coverage for school-based vaccination compared with vaccine delivery through health centers.[36 38]

Assuming long-life protection of HPV vaccines, 150 000 cervical cancer deaths would be prevented based on coverage estimates for 2014.[9] The estimation considers 70% effectiveness in all settings based on the worldwide HPV16/18 associated cervical cancer incidence. Accordingly, a greater number of cervical cancer deaths are projected to be averted for upper-middle income countries despite their lower coverage in comparison to high-income countries (Figure 2B). However, etiologic fractions of HPV16/18 are lower in populations with higher cervical cancer incidence and vice versa,[39] thereby making possible an increase in disparities in cervical cancer control if no action is undertaken to improve implementation of HPV vaccination in low- and middle-income countries.

The introduction of HPV vaccines in national immunization programs is taking longer than expected and the final availability is lower compared with the pace of introduction of other WHO recommendations, such as rotavirus and pneumococcal vaccines.[40] Several barriers have been described, including high prices, programmatic challenges in delivering to adolescents, low priority of cervical cancer, and global hesitancy.[34] Due to the lack of experience with adolescent vaccinations and concerns regarding vaccine acceptability, support from successful access models such as the Global Alliance for Vaccines and Immunization (GAVI) requests previous demonstrations of program capacity for HPV vaccine delivery, thereby reducing eligibility for HPV vaccine introduction of several low- and middle-income countries.

Indeed, a global market study by WHO found the lowest introduction in GAVI-eligible countries and middle-income countries non-eligible for GAVI or Pan American Health Organization (PAHO) support with an estimated global demand for 55 million doses in 2019 that would potentially reach 110 million annual doses by 2028.[41] The current supply is not sufficient and potential stressors such as a rapid multi-age cohort adoption in low- and middle-income countries, as well as catch-up vaccination, vaccination of boys, and increased capacity allocation to produce the nine-valent vaccine for high-income countries, might induce greater imbalance in the near future.

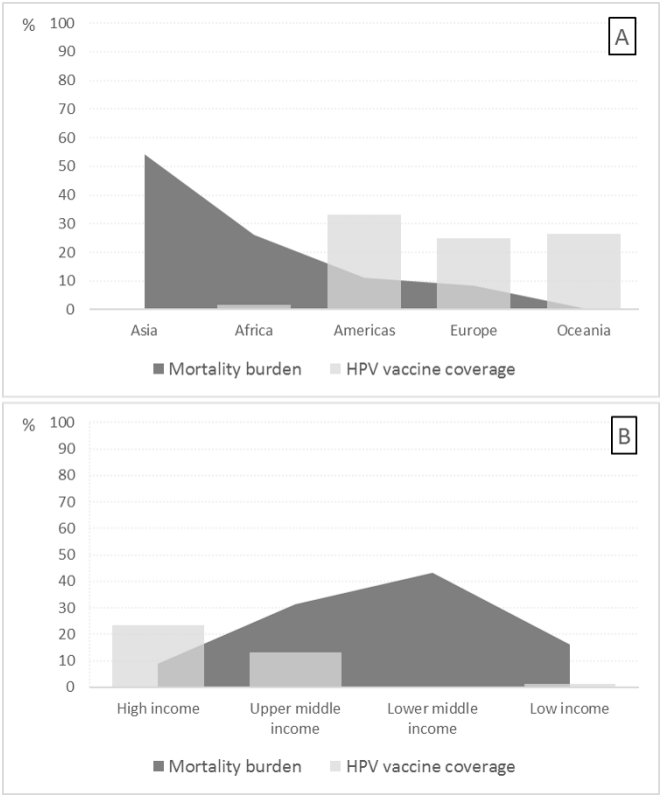

Figure 2 Human papillomavirus (HPV) vaccination coverage and burden of cervical cancer. Countries included in coverage estimates: Africa (Libya, Rwanda, Seychelles, Uganda, Lesotho, South Africa); Latin America and Caribbean (Barbados, Cayman Islands, Dominican Republic, Trinidad & Tobago, US Virgin Islands, Mexico, Panama, Argentina, Brazil, Chile, Colombia, Guyana, Paraguay, Peru, Suriname, Uruguay), Northern America (Bermuda, Canada, Greenland, USA); Asia (Kazakhstan, Japan, Bhutan, Brunei, Malaysia, Singapore, Israel, United Arab Emirates); Europe (Bulgaria, Czech Republic, Romania, Russian Federation, Denmark, Finland, Iceland, Ireland, Latvia, Norway, Sweden, UK, Gibraltar, Greece, Italy, Malta, Portugal, San Marino, Slovenia, Spain, Macedonia, TFYR, Austria, Belgium, France, Germany, Luxembourg, Monaco, Netherlands, Switzerland); Oceania (Australia, New Zealand, Fiji, New Caledonia, Guam, Kiribati, Marshall Islands, Micronesia, FS, N Mariana Islands, Palau, American Samoa, Cook Islands). Mortality burden corresponds to the percentage of cervical cancer deaths from worldwide estimates. HPV vaccine coverage corresponds to the estimated percentage of girls aged 10–14 years with a full course of vaccination in every setting. Sources: mortality[2]; coverage.[69]

Population-Level Effectiveness of HPV Vaccines

Several reports provide details on vaccine effectiveness from population-based analysis in immunization programs and surveillance systems (Table 3). Reports for the three available vaccines show

Table 3 Selected studies on population-level effectiveness of HPV vaccination (three doses) among primary target groups (pre-adolescent and adolescent girls)

Study	HPV vaccine	Country	Type of study	OR	95% CI
Prevalence of HPV vaccine types					
Cameron RL 2016[B1]	Bivalent	Scotland	Cross-sectional	0.27	0.19 to 0.37
Arbyn M 2016*[B2]	Bivalent and quadrivalent	Belgium	Cross-sectional	0.29	0.19 to 0.45
Tabrizi SN 2014[B3]	Quadrivalent	Australia	Cross-sectional	0.07	0.04 to 0.14
Spinner C 2019†[B4]	Nine-valent	USA	Cross-sectional	0.48	0.28 to 0.82
CIN2+ incidence/prevalence					
Palmer T 2019[B5]	Bivalent	Scotland	Retrospective cohort	0.11	0.06 to 0.19
Konno R 2018[B6]	Bivalent and quadrivalent	Japan	Retrospective	0.31	0.08 to 0.80
Verdoodt F 2019[B7]	Quadrivalent	Denmark	Retrospective cohort	0.40	0.33 to 0.49
Cervical cancer incidence					
Luostarinen T 2018[B8]	Bivalent and quadrivalent	Finland	Cohort	0.00	0.00 to 0.84
Guo F 2018[B9]	Not specified	USA	Cross-sectional	0.71	0.64 to 0.80

References B1 to B9 are available in the online supplemental material
*Restricted to HPV16/18.
†Compared with the quadrivalent vaccine and restricted to HPV types not included in the quadrivalent vaccine. Odds ratios (cross-sectional), prevalence ratios (retrospective), or incidence rate ratios (cohort) between vaccinated and non-vaccinated girls.
CIN, cervical intra-epithelial neoplasia; HPV, human papillomvirus.

a significant reduction in the prevalence of HPV vaccine types and reports for the bivalent and quadrivalent vaccines indicate a significant decline in CIN2 or worse. An interim analysis by the Finnish Cancer Registry reveals 100% efficacy for the prevention of invasive cancer.[42] In addition, a cross-sectional analysis with national data from the USA showed a 29% reduction in cervical cancer incidence among women aged 15–24 years when comparing pre- and post-vaccine periods with a possible combined effect of increased cervical cancer screening.[43]

All reports available in the field are from high-income countries, and we found no population-based information from low- and middle-income countries. The available data should be interpreted carefully given the sources of variability regarding population characteristics (CIN and cancer risk, HPV prevalence), program characteristics (age of vaccination, number of doses, vaccine coverage), and vaccine characteristics (HPV types, cross-protection). As previously stated, the potential impact of immunization against HPV16/18 might be slightly lower in low- and middle-income countries given the lower prevalence of associated disease in high-risk settings; however, the preliminary information available denotes great potential for the prevention of invasive cancer with variability primarily in the prevention of pre-cancerous lesions.

Herd immunity has been demonstrated by a reduced prevalence of HPV vaccine types and reduced incidence of genital warts in unvaccinated women.[44 45] With respect to the number of doses, a review of HPV vaccine effectiveness in 14 population-based studies observed the highest effectiveness with three doses; 11 out of 14 studies reported effectiveness for two doses, and six studies reported significant effectiveness for one dose. However, a variation in effectiveness by number of doses was observed for different endpoints (HPV prevalence, genital warts, and cervical disease) and age of vaccination (higher effectiveness for younger ages).[46] Similarly, population-level data confirm the effectiveness of catch-up vaccination in the prevention of cervical intra-epthelial neoplasia until a maximum age of 19–20 years but not for older ages, and higher protection against infection by non-vaccine types has been observed for women vaccinated at younger ages (<19 years old).[47 48] Data regarding population-level cross-protection are controversial; a study from Australia (quadrivalent vaccine) found no significant reduction in the prevalence of non-vaccine types after vaccination, while data from Scotland (bivalent vaccine) found a significant reduction in HPV 31, 33, and 45 as a group. However, a review of population-based studies with both vaccines found a reduced prevalence only for HPV 31 in individual analyses by HPV among women younger than 19 years, and an inconsistent increase after vaccination for other non-vaccine types.[49–51]

HPV Vaccine Safety

Side effects are the main source of controversy and hesitancy pertaining to HPV vaccination. The most common situation is individual or low-number reports on serious adverse events possibly related to the administration of HPV vaccines. Additionally, clustered reactions among vaccinated girls have occurred in different countries (Colombia, Denmark, and Japan), thus contributing to the controversies surrounding vaccine safety. At least five metanalyses have been published during the last 5 years; however, none of them has cited a significant association between the bivalent, quadrivalent or nine-valent vaccines with autoimmune disease, demyelinating disease or any other serious systemic adverse event (Table 4). Although the vast majority found no association, systematic reviews without metanalytic data are more controversial, with some highlighting a higher frequency of adverse events in vaccinated populations but lacking clarity in the analysis of local versus serious systemic adverse events.[52]

Recently, published metanalyses have drawn strong criticism around conflict of interests and deficient scientific rigor in search strategies to include all possible sources of information on adverse events, counting public but not published data from clinical trial

Table 4 Selected metanalysis on HPV vaccine safety

Author	Side effects	OR	95% CI
Mouchet J *et al*[C1]	Demyelinating diseases	0.96	0.77 to 1.20
Setiawan D *et al*[C2]	Systemic in Asian populations	1.33*	1.18 to 1.50
Arbyn M *et al*[C3]	Serious adverse events	1.01	0.95 to 1.07
Genovese C *et al*[C4]	Autoimmune disease	1.04	0.69 to 1.56
Costa APF *et al*†[C5]	Dizziness	1.09	0.93 to 1.27
	Fatigue	1.09	0.91 to 1.30
	Pruritus	1.44	1.26 to 1.65
	Gastrointestinal symptoms	1.24	1.09 to 1.45
	Headache	1.07	0.99 to 1.15
	Fever	1.18	1.06 to 1.36
Gonçalves AK *et al*[C6]	General symptoms	Bivalent 1.07	0.82 to 1.41
		Quadrivalent 1.11	1.00 to 1.23

References C1 to C6 are available in the online supplemental material
*OR value considered not relevant for the risk-benefit balance by authors. Systemic symptoms with significant difference in Asian populations correspond to arthralgia and myalgia.
†Nine-valent vaccine compared with quadrivalent vaccine.
HPV, human papillomavirus.

registries and post-licensure registries.[53] Beyond methodological considerations for systematic reviews on the subject, and based on the considerable amount of information from public health systems around the world with over 270 million doses already delivered, the WHO states the risk of anaphylaxis is approximately 1.7 cases per million doses, and found no association of HPV vaccines with Guillain-Barre syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, or any other medically relevant condition.[54] More recently, new reports based on the Vaccine Adverse Events Reporting System (VAERS) from the USA confirm the lack of association between the quadrivalent and bivalent vaccines with any serious adverse event.[55 56]

Similarly, governmental reports on clustered reactions in Denmark (postural orthostatic tachycardia syndrome) and Colombia (mass psychogenic illness) did not identify an association with HPV vaccination.[57 58] An English-language version is not available of the report by the Japanese Ministry of Health, Labor and Welfare regarding the events that led to suspending the proactive recommendation of HPV vaccinations in that country; however, a population-based study commissioned by the municipality of Nagoya found no association between the reported symptoms and HPV vaccination.[59] Despite the convincing evidence of the nature of cluster reactions and the lack of scientific support for its association with HPV vaccines, vaccination coverage has dramatically dropped in these countries and remains significantly lower than the initial uptake.[59–61] A recent analysis from social media found a higher number of clustered-anxiety reactions in national immunization programs than reported in the literature (18 in total); all related to school vaccination and 48.7% related to HPV vaccines.[62] Given the advantages of school vaccination, adequate preparedness for an effective response to adolescents' and parents' questions, management of potential adverse events, and prevention of massive reactions should be mandatory before HPV vaccine introduction.

A structured evaluation of the role of media in these particular situations is not available. A systematic review observed the trend of a higher percentage of positive messages about HPV vaccination in social media in recent years and a correlation between vaccine coverage and community exposure to informed media news (positive association) or exposure to safety concerns in social media (negative association). Exposure to positive content in social media, however, was correlated with greater awareness but not with higher vaccine uptake.[63]

CONCLUSIONS

Cervical cancer remains a relevant public health problem, particularly in low- and middle-income countries, and HPV vaccines provide the most promising alternative for disease control; however, their introduction is slow in countries with greater need. A significant amount of evidence is currently available from both clinical and population-based studies, thereby reducing uncertainty regarding vaccine effectiveness and safety. While interesting from a methodological perspective, the discussion on side effects may be immaterial from a public health perspective since the analysis from surveillance systems with millions of doses distributed has found no association of HPV vaccination with serious systemic side effects (Table 4). However, monitoring of HPV vaccine safety should continue and reporting adverse events after vaccine delivery should remain the foundation of vaccine safety.[17] Even with a reduced uncertainty regarding efficacy, effectiveness, and safety, the implementation of HPV vaccination in national immunization programs remains a primary challenge to tackling cervical cancer. Alternative approaches such as one-dose schedules or vaccination of children under 5 years old can help reduce programmatic and economic challenges to adolescent vaccination. While the former is currently under evaluation in clinical trials, the latter has not raised enthusiasm for clinical research. This lack of interest is perhaps due to

uncertainties in duration of protection and requirements by regulatory agencies to license HPV vaccines for this age group.

Our review does not address several topics in HPV vaccines such as the vaccination of males and high-risk populations and the impact on outcomes different from cervical neoplasia. The quadrivalent and nine-valent vaccines have demonstrated efficacy against vulvar, vaginal, and anal intra-epithelial neoplasia; consequently, they are licensed for the prevention of related cancers.[64] Despite the etiological association with other cancer types, an evaluation of HPV vaccine efficacy on their prevention has not been undertaken to date.

Cost-effectiveness of HPV vaccination has been consistent in economic evaluations across different settings, and the inclusion of a broader spectrum of HPV-related cancers indicate greater benefits, particularly for vaccination in males. However, due to the lack of information on the efficacy of HPV vaccines for several associated cancer types, many models rely on sound theoretical principles rather than on clinical evidence.

The available evidence on HPV vaccine efficacy, effectiveness, safety, and cost-effectiveness is sufficient and strong enough to support proper decision-making; however, implementation challenges might benefit from new knowledge obtained through implementation research.

Additional references can be found in the online supplementary appendix.

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