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Making HPV vaccination available to girls everywhere

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Abstract

Cervical cancer is currently the fourth leading cause of cancer death among women worldwide, with most cases occurring in low- and middle-income countries. Safe, highly effective vaccines against human papillomavirus (HPV) have been on the market since 2006, yet only 6% of girls worldwide have received this life-saving cancer prevention intervention. International organizations, including PATH, Gavi, and the pharmaceutical companies Merck and GlaxoSmithKline, have provided support to eligible low- and middle-income countries to implement national HPV vaccination programs. Still, glaring disparities in the availability of national HPV vaccination programs and the coverage of the primary target population between the global north and south persist. We illustrate worldwide HPV vaccine implementation and coverage using an online data visualization, which is publicly available and can be used to gain unique insights. We also present three emerging solutions to transform future HPV vaccine delivery in low- and middle-income countries: low-cost generics, single-dose vaccination, and co-administration with other adolescent vaccines. By rapidly expanding access to HPV vaccination to girls everywhere, vaccine-type HPV infections can be virtually eliminated. At high vaccination-

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Author contributions

AMO and CJC conceptualized and outlined the manuscript. AMO drafted and coordinated edits to the manuscript. AMO, LR, LC, NMF, and CJC provided critical input on drafts of the manuscript and approved of the final version of the manuscript for publication.

Conflict of interest

The authors have no conflicts of interest.

coverage levels, more than 80%—or approximately 230 000—of the cervical cancer deaths that occur each year can be averted.

Keywords

Cervical cancer prevention; Co-administration; Coverage; Dosing schedule; Human papillomavirus; Impact; Low- and middle-income countries; Vaccination

1 Introduction

Cervical cancer, almost entirely attributable to human papillomavirus (HPV), is the fourth leading cause of cancer in women worldwide [1]. The vast majority of the 528 000 new cases and 266 000 cervical cancer deaths reported each year occur in low- and middle-income countries (LMICs) among women whose access to cervical cancer screening, treatment, and palliative care is either limited or nonexistent [1]. To date, the benefits of primary prevention—vaccination against HPV—are also largely unrecognized in LMICs.

Three prophylactic HPV vaccines are currently licensed to prevent preinvasive and invasive cancer of the cervix, vagina, and vulva caused by vaccine-type HPV infections. The first, quadrivalent Gardasil (4vHPV; Merck, Whitehouse Station, NJ, USA), was approved by the US Food and Drug Administration (FDA) in 2006 and received WHO prequalification in 2009. Two additional FDA-approved vaccines, bivalent Cervarix (2vHPV; GlaxoSmithKline, London, UK) and nonavalent Gardasil 9 (9vHPV, Merck), were subsequently prequalified by the WHO in 2009 and 2018, respectively. All three vaccines comprise recombinant L1 capsid proteins, which self-assemble into virus-like particles that resemble the HPV virion but lack HPV DNA and thus are noninfectious. The vaccines differ in the HPV types' L1 capsid proteins they contain and in the adjuvant used. Human papillomavirus types 16 and 18, which account for 71% of all cervical cancers worldwide, are covered by all three vaccines, whereas types 31, 33, 45, 52, and 58, found in 9vHPV, account for an additional 19% of all cervical cancers (Figure 1) [2]. Prophylactic vaccines have been evaluated in more than 75 000 women and men in clinical trials conducted globally with up to 10 years of follow-up. All three are highly immunogenic, efficacious, and safe (Table 1) [3–5]. Importantly, their immunogenicity and safety have also been demonstrated in HIV-infected individuals, who are at two- to five-fold increased risk of HPV-associated anogenital cancers [6].

In a combined analysis of four randomized controlled trials of 4vHPV enrolling more than 20 000 women, vaccination reduced the risk of HPV-16/18-related cervical intraepithelial neoplasia (CIN) 2/3+ (defined as CIN2/3, adenocarcinoma in-situ, or invasive cervical cancer) by 99% among HPV-naïve women [7]. Similarly, in the PApilloma TRIal against Cancer In young Adults (PATRICIA) of 2vHPV, HPV-16/18-related CIN3+ was reduced by 93% in an HPV-naïve population [8]. In a phase 3 trial of 9vHPV, this vaccine led to a 97% reduction in the combined incidence of HPV-31/33/45/52/58-related high-grade cervical, vaginal, and vulvar disease compared with 4vHPV [9]. Additionally, when compared with 4vHPV, 9vHPV demonstrated noninferior antibody responses to HPV-6/11/16/18 [9,10]. The 4v- and 9vHPV vaccines also reduce the incidence of HPV-6/11-related genital warts by

99% among HPV-naïve women [4,5]. Sustained immunogenicity (up to 10 years) is achieved with all three vaccines, and the rates of serious adverse events such as anaphylaxis and autoimmune syndromes are low (0.2%–0.4%) [11,12]. Moreover, among 18 000 women from three trials with nearly 100 000 patient-years of follow-up, no cases of cervical cancer were reported in the vaccinated group [13].

Current WHO recommendations endorse nationwide HPV vaccination programs targeting girls aged 9–14 years [12]. The rationale for focusing on preadolescent and adolescent girls is that vaccine efficacy declines considerably among women previously exposed to HPV. Although per-protocol analyses from, for example, the FUTURE II (4vHPV) and PATRICA (2vHPV) trials demonstrate a strong protective effect of vaccination (93%–99%), the efficacy was substantially lower (44%–46%) in the intention-to-treat analyses, which included girls with prior HPV infection [7,8]. However, HPV vaccines remain highly efficacious in women up to 45 years of age who have not previously been infected with HPV [14,15]. Targeting older girls and women—or targeting males—is therefore recommended if doing so does not divert resources away from the primary target group. Because no vaccine has shown superior efficacy in preventing cervical cancer, the WHO recommends the choice of HPV vaccine be made based on the local context.

2 Projected impact of HPV vaccination

If implemented at scale, HPV vaccination will likely prevent millions of deaths from cervical cancer, particularly in LMICs. The primary evidence for reductions in cancer incidence and mortality attributable to HPV vaccination is derived from epidemiologic models; we highlight five such models here, focusing on cervical cancer outcomes (Table 2).

The Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model, published in 2014 [16], evaluates the potential impact of HPV-16/18 vaccination of 58 million 12-year-old girls in 179 countries. The model estimates that 690 000 cases and 420 000 deaths from cervical cancer could be prevented over the life of the cohort, at a cost of US$4 billion. Countries that did not have national HPV vaccination programs at the time the model was developed are projected to realize the largest reductions in cervical cancer cases. As such, most benefits are expected to accrue in LMICs, where 655 000 of 690 000 (95%) cervical cancer cases and 404 000 of 420 000 (96%) deaths would be averted with vaccination. The PRIME vaccination strategy is also noted to be very cost-effective (based on the commonly used cost-effectiveness threshold, gross domestic product [GDP] per capita) in 156 (87%) of 179 countries [16].

The realization of this important public health benefit is dependent on achieving high vaccine coverage levels. A model developed Van Kriekinge et al. and published in 2014 [17] illustrates the effect of varying levels of HPV-16/18 vaccination coverage on the incidence and mortality of cervical cancer. Using estimates of 2vHPV efficacy in HPV-naïve girls [8], this model assumes that HPV vaccination will be 93% protective against HPV-16/18 and also takes into account cross-protection afforded against other HPV types. At vaccine coverage rates of 50%, 246 000 cervical cancer cases and 127 000 cancer deaths worldwide

would be averted each year. If coverage rates were increased to 90%, 443 000 cases and 229 000 deaths would be averted [17].

Two additional models focus on LMICs specifically. The first, published in 2008 by Goldie et al. [18], estimates the population level impact of HPV-16/18 vaccination in 72 countries eligible for Gavi support at the time the model was developed. Measuring 10 consecutive LMIC birth cohorts, Goldie et al. estimate that 3 million cervical cancer deaths would be prevented. This corresponds with reductions in the lifetime risk of cervical cancer ranging from 27% in Bolivia to 60% in Ethiopia, with the variation in projected impact resulting from underlying differences in the proportion of cervical cancers caused by HPV-16/18 in each region [18]. The second, by Kim et al. [19], estimates the impact of vaccination in five consecutive birth cohorts in 48 Sub-Saharan African countries. In this model, 670 000 cases of cervical cancer would be prevented. Reductions in cases averted per 1000 girls vaccinated ranged from five in Sudan to 35 in Guinea. Kim et al. also compare the cost-effectiveness of various cervical cancer screening strategies alone and in combination with a preadolescent HPV vaccination program. In Uganda and South Africa, the countries included in this portion of the analysis, the addition of HPV DNA testing three times in a lifetime (at 35 years, 40 years, and 45 years) resulted in an additional 12%–13% reduction in the lifetime risk of cervical cancer. However, the combination strategy was noted to be less cost-effective than the provision of HPV vaccination alone [19].

The choice between 2v-, 4v-, and 9vHPV is an important decision for policymakers, who must balance the projected program impact against cost considerations within the context of local epidemiologic trends and competing health priorities. A 2012 model by Van de Velde et al. [20] provides useful insight by estimating the reductions in the cervical cancer incidence following 2v-, 4v-, or 9vHPV vaccination. In this model, 2vHPV is associated with greater reductions in the cervical cancer incidence than is 4vHPV (62% versus 59%) because of the higher cross-protective efficacy of 2vHPV. However, switching from 4vHPV to 2vHPV would only prevent an additional 3% of CIN2/3 cases over a 70-year period and would result in a 63% increase in anogenital warts. By contrast, switching from 2v- or 4vHPV to 9vHPV is estimated to reduce the incidence of CIN2/3 by 9%–13% over the long term because of the coverage of additional high-risk HPV types [20].

Although epidemiologic models are helpful in framing programmatic and policy discussions, it is important to note that such models are limited by the quality of the data available for the parameter estimates and by their underlying assumptions. The data available on HPV vaccination, especially as they relate to LMICs, are of relatively poor quality. Additionally, all five models assume that vaccination confers lifelong protection against HPV infection, despite the fact that only 10 years of follow-up data are available from clinical trials [6,11]. With the exception of Van de Velde et al. [20], all authors assume 100% efficacy, whereas efficacy rates around 95% are likely more realistic [3–5]. These assumptions may have led to an overestimation of the population level impact of HPV vaccination strategies. On the other hand, only two of the five models account for cross-protection or herd immunity, which may have resulted in underestimations by the other authors, who do not consider the possible elimination of HPV-16/18 at vaccination coverage rates of 80% or more [21]. Finally, only Van de Velde et al. [20] account for both the

dynamic transmission of HPV (new infections over time) and the effects of screening and treatment on the incidence and mortality of cervical cancer.

3 HPV vaccine implementation and coverage in LMICs

To better illustrate worldwide HPV vaccine implementation and coverage, we have created an online data visualization tool using Tableau software (Seattle, WA, USA) (available at https://public.tableau.com/views/HPVVaccineReviewV3_0/NationalandDemoProgramsalltime2?:embed=y&:useGuest=true&:display_count=yes). The visualization contains data from 189 countries and includes demonstration projects and national HPV vaccination programs implemented between 2006 and 2018. The online visualization also allows users to manipulate our data to gain unique insights, providing an advantage over static figures.

4 Vaccine implementation support

Over the past decade, several international organizations, including PATH, Gavi, and the pharmaceutical companies Merck and GlaxoSmithKline, have supported HPV vaccination efforts in LMICs. Between 2007 and 2010, PATH partnered with the governments of India, Peru, Uganda, and Vietnam to carry out small-scale demonstration projects with the goal of providing evidence for nationwide scale-up [22]. Additionally, the Merck Gardasil Access Program (GAP) funded 31 demonstration projects in 21 LMICs between 2009 and 2014 [23]. Merck also donated vaccine to Bhutan and Rwanda to support national school-based programs in 2010 and 2011, respectively. As the first LMICs to establish national HPV vaccination programs, Bhutan and Rwanda provide key lessons on rapid program implementation while sustaining high vaccine coverage rates [24].

In 2012, Gavi announced a landmark deal to purchase HPV vaccines from the manufacturers at US$4.50–4.60 per dose. Eligible countries (gross national income per capita less than US $1,500, averaged over the past 3 years and adjusted for inflation) could apply for support to implement HPV vaccination demonstration projects. Successful applicants received subsidized vaccine at US$0.20–4.50 per dose and a one-time vaccine introduction grant of US$2.40 per eligible girl [25].

With deeply discounted vaccine available through PATH, GAP, Gavi, and other initiatives launched between 2007 and 2016, demonstration projects have now been conducted in 50 countries (30 supported by Gavi, 22 by GAP, and 11 by other organizations including PATH) [26–28]. Of these, however, only 15 (30%) countries have gone on to establish national HPV vaccination programs (Figure 2A and Figure 2B; see online data visualization). Many pilot projects have therefore fallen short of their intended goal of informing national vaccine implementation.

Gavi-eligible countries (https://www.gavi.org/results/countries-approved-for-support/) can currently apply for assistance implementing national HPV vaccination programs with or without experience from prior demonstration projects (Figure S1) [29]. This decision to support the introduction of nationwide programs—rather than demonstration projects—may help to facilitate HPV vaccination scale-up in 18 of the world’s poorest countries with no

prior history of demonstration projects. The Pan American Health Organization has provided subsidized HPV vaccine for national programs since 2008 at US$8.50 per dose [30], which may be one reason why Latin America and the Caribbean have the highest proportion of countries with national HPV vaccination programs (see online data visualization). Gavi's new model could support countries in implementing HPV vaccination programs in much the same way.

5 National HPV vaccination programs

Figure 3A illustrates the chronology of national HPV vaccination program implementation worldwide (a detailed timeline can be found in the online data visualization). By the end of 2017, more than 10 years after the first HPV vaccine was approved by the FDA, only 40% of government health agencies had implemented national HPV vaccination programs. Of the 78 national programs currently in existence, 2 are in low-income countries (7% of all low-income countries), 10 in low-middle-income countries (19%), 26 in upper-middle-income countries (50%), and 40 in high-income countries (77%) (Figure 3B; Figure S2). Initial disparities between high-income countries and LMICs were largely attributable to vaccines costs, which are variable in the public sector and comprise up to US$100 per dose in the private sector. However, several recent policy advances and falling prices provide renewed hope of access to HPV vaccination for many young women. In early 2018, 14 additional countries announced plans to implement national HPV vaccination programs. Of these, eight are LMICs that have previously conducted demonstration projects supported by Gavi and/or GAP.

To achieve maximal benefit, HPV vaccination programs must ensure high coverage levels in the target population. In LMICs, this is typically preadolescent girls aged 9 years and older [21]. Figure 4A and Figure 4B illustrate major public health failures to achieve adequate vaccine coverage in both rich and poor countries. Although data are sparse and may also be of poor quality, we note wide variation in full-course vaccine coverage, defined as the proportion of girls in the target population receiving two or three doses of vaccine. Among 50 countries with publicly available coverage data from national HPV vaccination programs, the median full-dose coverage was 68% (interquartile range, 46%–84%); the results ranged from 8% in Ecuador to 97% in Botswana and Rwanda [31–35]. Acceptability of the HPV vaccine is also an important factor in achieving high vaccine coverage and should be addressed contemporaneously with structural barriers to vaccine access [36].

6 Expanding access to HPV vaccination in LMICs

Global progress in the primary prevention of cervical cancer remains suboptimal. Only 6% (or 47 million) of all 10–20-year-old young women worldwide have received the full course of an HPV vaccine (Figure 5). Resource-constrained countries in Africa and Asia currently lag the furthest behind; here, only 1% (or 6 million) of the young women have been vaccinated [31]. Possible solutions include: low-cost generics, single-dose vaccination, and co-administration with other adolescent vaccines. Each of these changes could lower the barrier—in cost and human capital—to making HPV vaccination available in LMICs. As

HPV vaccination becomes cheaper and easier to provide, programs may also expand to include the vaccination of older girls and women [37].

6.1 Generic HPV vaccines

The introduction of generic HPV vaccines could immediately disrupt the global market, providing access to affordable vaccines for national programs. Although Gavi's negotiated price of US$4.50 per dose is well below the market price, the true manufacturing costs are estimated at US$2.07–3.05 per dose for the first set manufactured in a given year, because of high fixed costs, but are at only US$0.48–0.59 per dose for a second set [38]. Both of these estimates are well below the lowest known negotiated prices for 4vHPV of approximately US$12 in Brazil and South Africa and also significantly below Gavi's negotiated price [38]. Manufacturers in LMICs, including in Brazil, China, and India, currently produce high-quality generic vaccines for the international market, supplying approximately half of all vaccines procured by Gavi [39]. A technology transfer agreement between Merck and a Brazilian company that will produce a vaccine for its domestic market is already in place. Other LMIC vaccine manufacturers are reportedly negotiating agreements as well [24].

With the patent on 4vHPV expiring in 2021, opportunities to promote the development of generic HPV vaccines in LMICs are both timely and imperative. Nevertheless, this approach is unlikely to result in a substantial improvement in access to vaccination on its own. Modeled estimates of manufacturing costs may underestimate the real-world costs of producing a generic HPV vaccine. Additionally, the vaccine costs represent only a portion of the total cost of introducing a new vaccination program. Public health systems also incur expenses related to training, vaccine administration, health education, and social mobilization. An analysis of demonstration projects in 12 countries found that, over and above the HPV vaccine costs, the average cost per dose was US$8.30. However, roughly half of this amount was attributed to introduction costs. Therefore, as programs mature, the additional cost per dose is anticipated to fall [40].

6.2 Single-dose HPV vaccination

All available HPV vaccines are currently approved as a two-dose series in girls younger than 15 years of age and a three-dose series in girls 15 years or older, with the doses given over a period of at least 6 months [12]. If proven effective, single-dose HPV vaccination (without the need for a booster dose) would be simpler and more affordable than current dosing schedules, decreasing the burden on public health systems in LMICs [41]. Switching to a single-dose schedule is also anticipated to increase vaccination coverage levels (Figure S3). Current estimates from national programs indicate that the median coverage drops from 85% (interquartile range, 46%–84%) for single-dose vaccination to 68% (interquartile range, 61%–89%) for two- or three-dose vaccination [31].

Emerging evidence to support this approach includes an observational cohort study conducted in India [42], in which the immunogenicity (measured by geometric mean avidity) for one dose of 4vHPV was noninferior to that for three doses. After nearly 5 years of follow-up, the risk of HPV-16/18 infection reported among girls in the one-dose vaccine group compared with those in the three-dose group was similar (1.1% versus 0.4%).

Additionally, a post-hoc analysis of two 2vHPV trials found that 4 years after vaccination, the efficacy against HPV-16/18 was 77% for three doses and 86% for one dose of the vaccine (P=0.36) [43]. The Costa Rica Vaccine Trial Group has demonstrated no significant differences in cumulative HPV infections between one, two, and three doses of the 2vHPV vaccine [44]. The group is currently conducting a randomized trial to determine the efficacy of one- and two-dose schedules of the 2vHPV and 9vHPV vaccines in girls and women aged 12–20 years (ClinicalTrials.gov: NCT03180034).

As evidence and enthusiasm for single-dose HPV vaccination evolves, special consideration will be required for HIV-infected individuals, for whom only the three-dose HPV vaccine schedule is currently recommended [12]. This is of great significance to policymakers in Sub-Saharan Africa, where many countries are experiencing generalized HIV epidemics with large numbers of HIV-infected young women, whose lifetime risk of cervical cancer is substantial.

6.3 Co-administration of the HPV vaccine

Co-administration of the HPV vaccine with other routine adolescent vaccines (Figure 6) would further simplify vaccine delivery and reduce the burden on public health systems and families. A systematic review of nine studies published between 2008 and 2012 found that both 2vHPV and 4vHPV can be safely co-administered with a variety of adolescent vaccines including meningococcal conjugate (MCV4); hepatitis A; hepatitis B; combined hepatitis A and B; tetanus, diphtheria, acellular pertussis (Tdap); and inactivated poliovirus vaccines [45]. All but one of the included studies demonstrated noninferior immune responses (defined by seroconversion rates and geometric mean titers of antibodies) to all vaccine components. Arguedas et al. [46] demonstrated inferior immune responses to portions of the Tdap and MCV4 vaccines when co-administered with the HPV vaccine, but four other studies found noninferior responses to these vaccine components. Although eight of the nine studies in the systematic review were open-label investigations and the reporting on adverse events was inconsistent across studies, no significant increases in local or systemic reactions were noted [45].

7 Conclusion

Despite its potential for a far-reaching impact, HPV vaccination remains out of reach for more than 90% of girls worldwide. By the end of 2017, only 78 countries had implemented national HPV vaccination programs and full-dose coverage levels in these programs are, on average, suboptimal. Countries in the LMIC category experience a disproportionate burden of cervical cancer incidence and mortality; yet, in most, the implementation of national HPV vaccination programs is either delayed or completely stalled.

Competing health priorities, relatively high vaccine costs, and a dosing schedule that does not conform to traditional early childhood immunizations create hurdles to HPV vaccine implementation in the countries where it is most needed. The present review outlines three emerging solutions to address this public health failure: low-cost generics, single-dose vaccination, and co-administration with other adolescent vaccines. Using existing vaccine technology, these solutions have the potential to transform future HPV vaccine delivery in

LMICs. By acting now and making HPV vaccination available to girls everywhere, a million cervical cancer deaths will be averted over the next decade.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

An accompanying online data visualization tool is available for this article at https://public.tableau.com/views/HPVVaccineReviewV3_0/NationalandDemoProgramsalltime2?:embed=y&:useGuest=true&:display_count=yes

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Synopsis:

Despite its potential for far-reaching impact, HPV vaccination remains out of reach for most girls. Transforming vaccine delivery paradigms could address this public health failure.

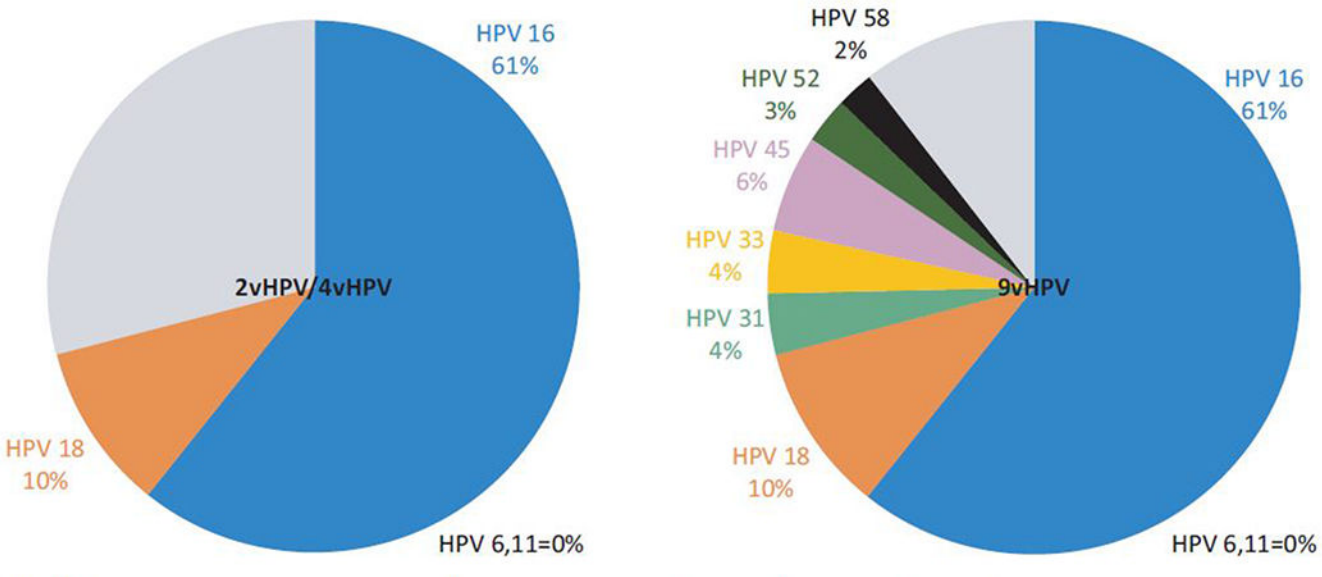
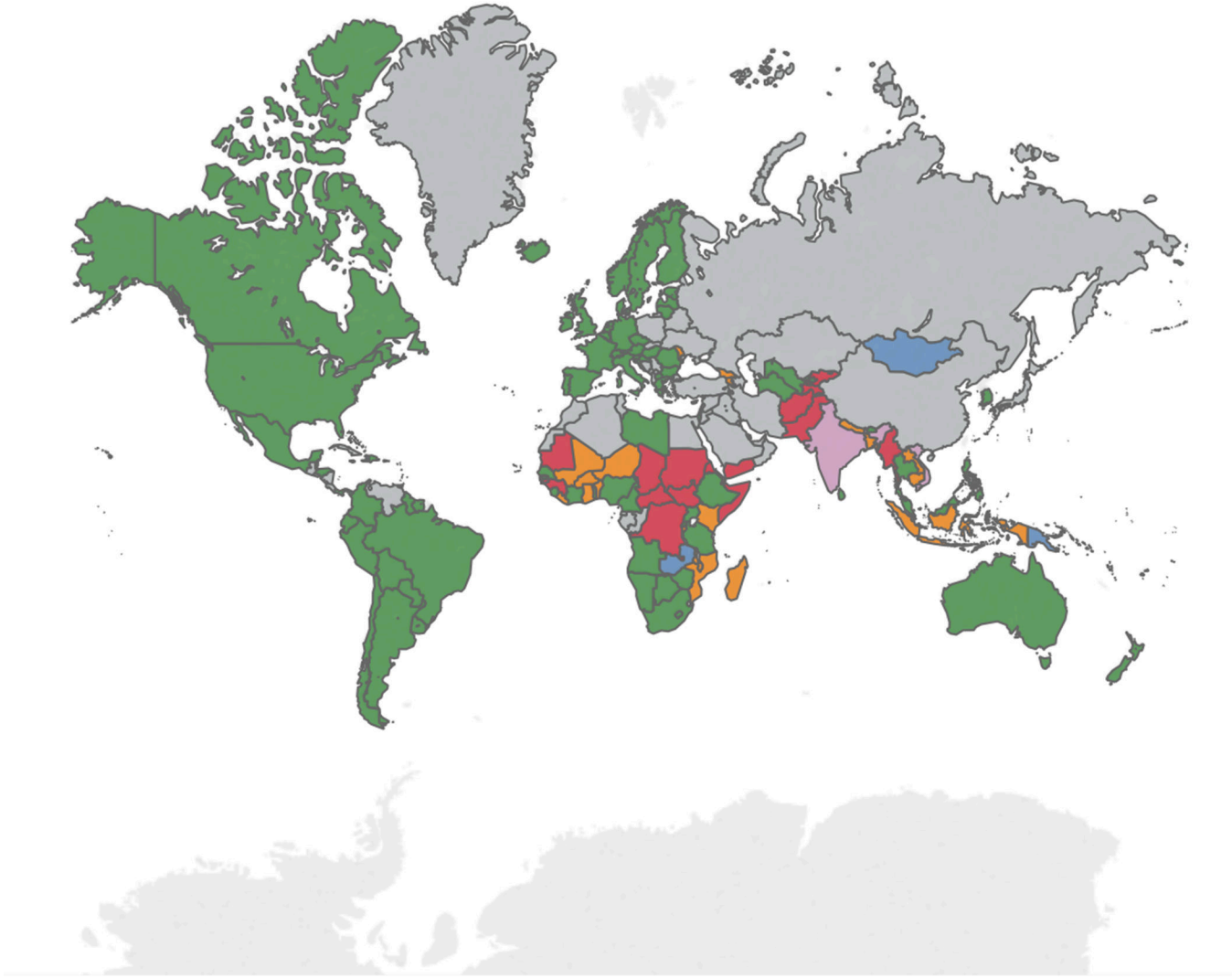


Figure 1.

Proportion of cervical cancers attributable to vaccine-type human papillomavirus infections. Abbreviations: 2vHPV, bivalent vaccine; 4vHPV, quadrivalent vaccine; 9vHPV, nonavalent vaccine; HPV, human papillomavirus.



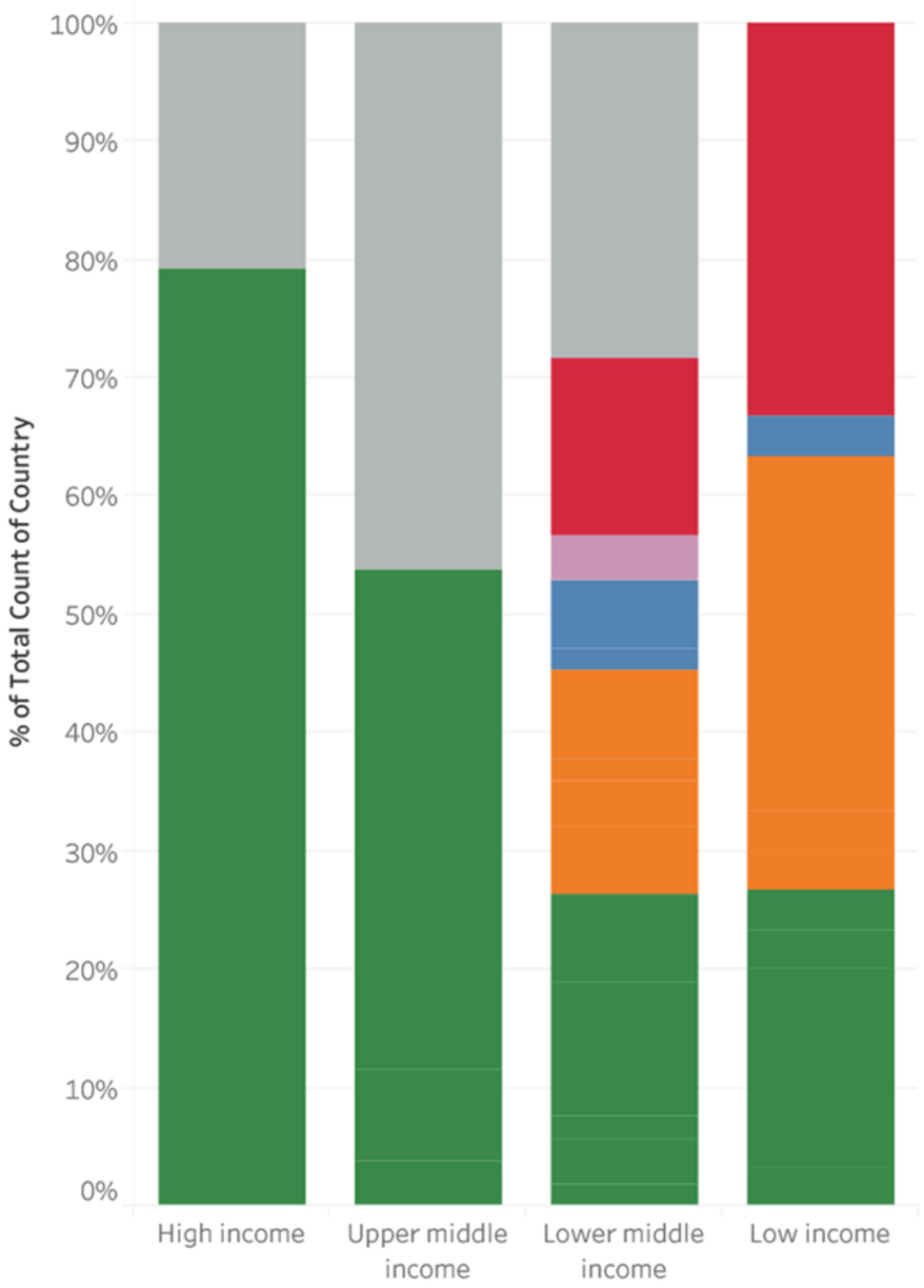
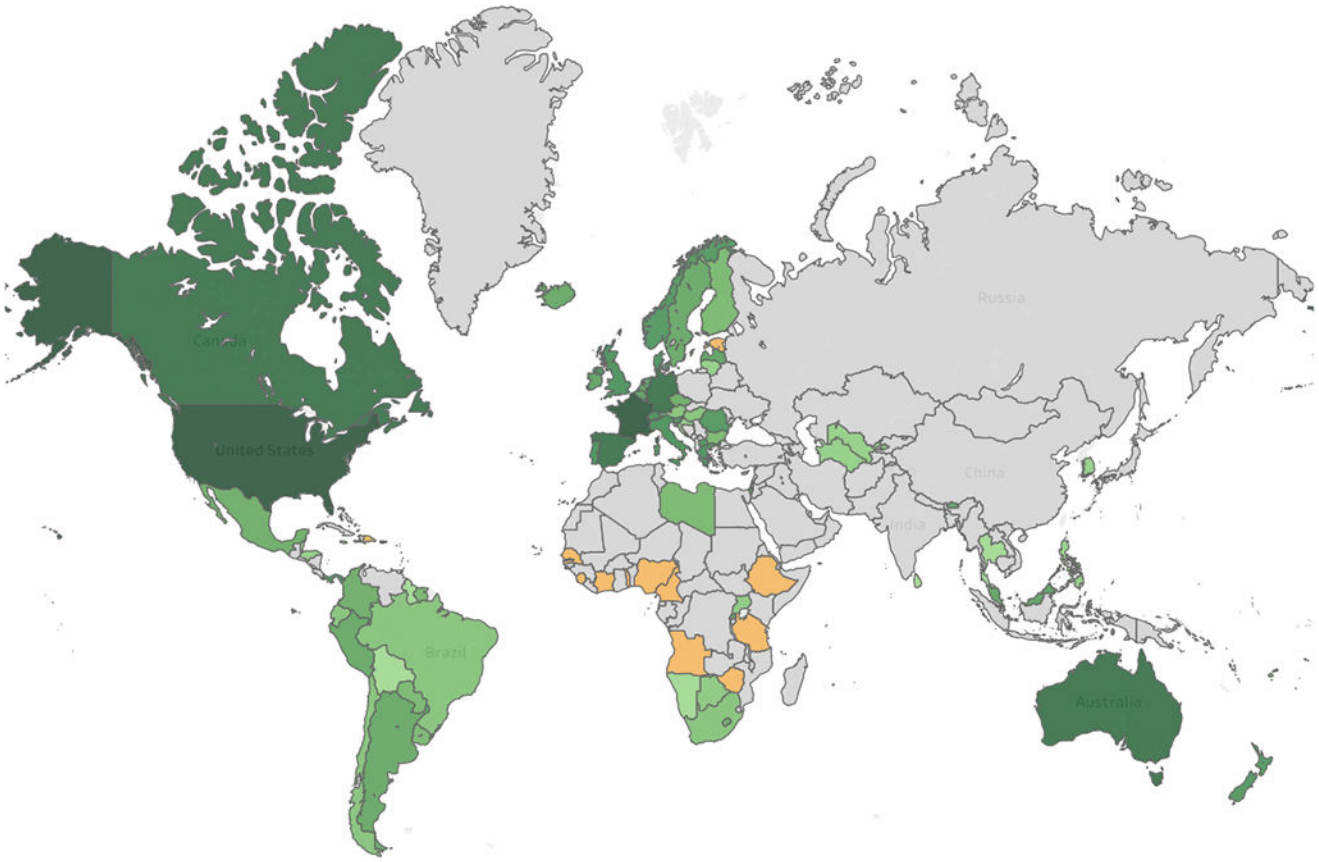


Figure 2.

Worldwide distribution of human papillomavirus vaccination programs (2006–2017) (A). Proportion of countries with national human papillomavirus vaccination programs and demonstration projects by income group (2006–2017) (B). Green indicates countries with a national program, orange indicates a Gavi program, blue indicates a GAP program, violet indicates another demonstration program, red indicates eligibility for Gavi but no program, and gray indicates no program. Note: countries that have conducted multiple demonstration projects or have conducted demonstration projects prior to the introduction of a national

program are labeled based on the program with the broadest reach. A national program is defined as any government policy or program that promotes broad access to human papillomavirus vaccines. The World Bank defines the income groups by gross national income per capita as: low income, US$1,005 or less; lower middle income, US$1,006–3,955; upper middle income, US$3,956–12 235; and high income, US$12 236 or more. An interactive version of this map is available (https://public.tableau.com/views/HPVVaccineReviewV3_0/NationalandDemoProgramsalltime2?:embed=y&:useGuest=true&:display_count=yes).



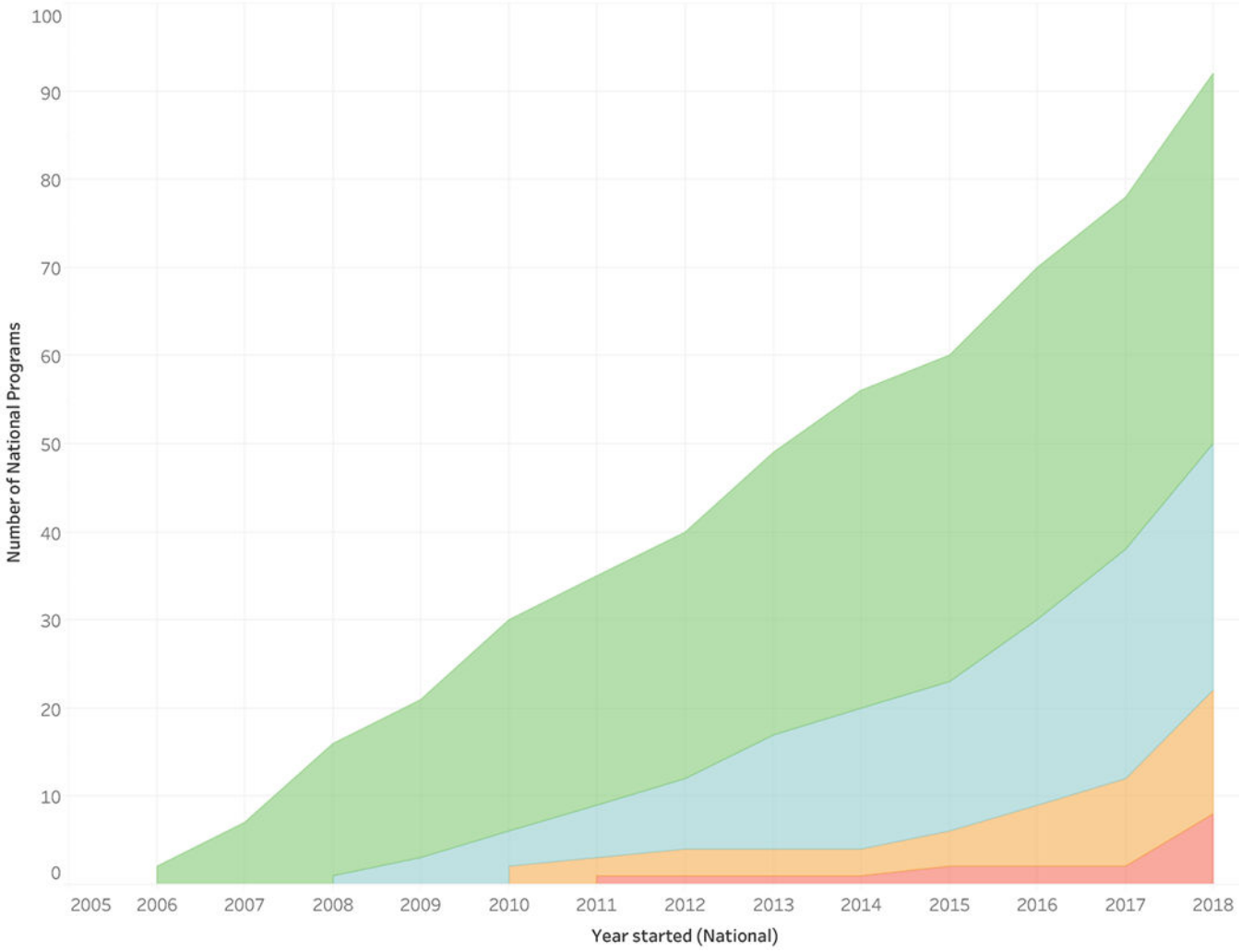


Figure 3.

Worldwide distribution of human papillomavirus vaccination programs by year of implementation (A); darker shades of green indicate earlier implementation (from 2006), lighter shades of indicate more recent implementation (until 2017), and orange indicates 2018 and planned implementation. Proportion of countries with national human papillomavirus vaccination programs by income group (B); green indicates high income, blue indicates upper middle income, orange indicates lower middle income, and red indicates low income. Note: A national program is defined as any government policy or program that promotes broad access to human papillomavirus vaccines. The World Bank defines the income groups by gross national income per capita as: low income, US$1,005 or less; lower middle income, US$1,006–3,955; upper middle income, US$3,956–12 235; and high income, US$12 236 or more. An interactive version of this map is available (https://public.tableau.com/views/HPVVaccineReviewV3_0/NationalandDemoProgramsalltime2?:embed=y&:useGuest=true&:display_count=yes).

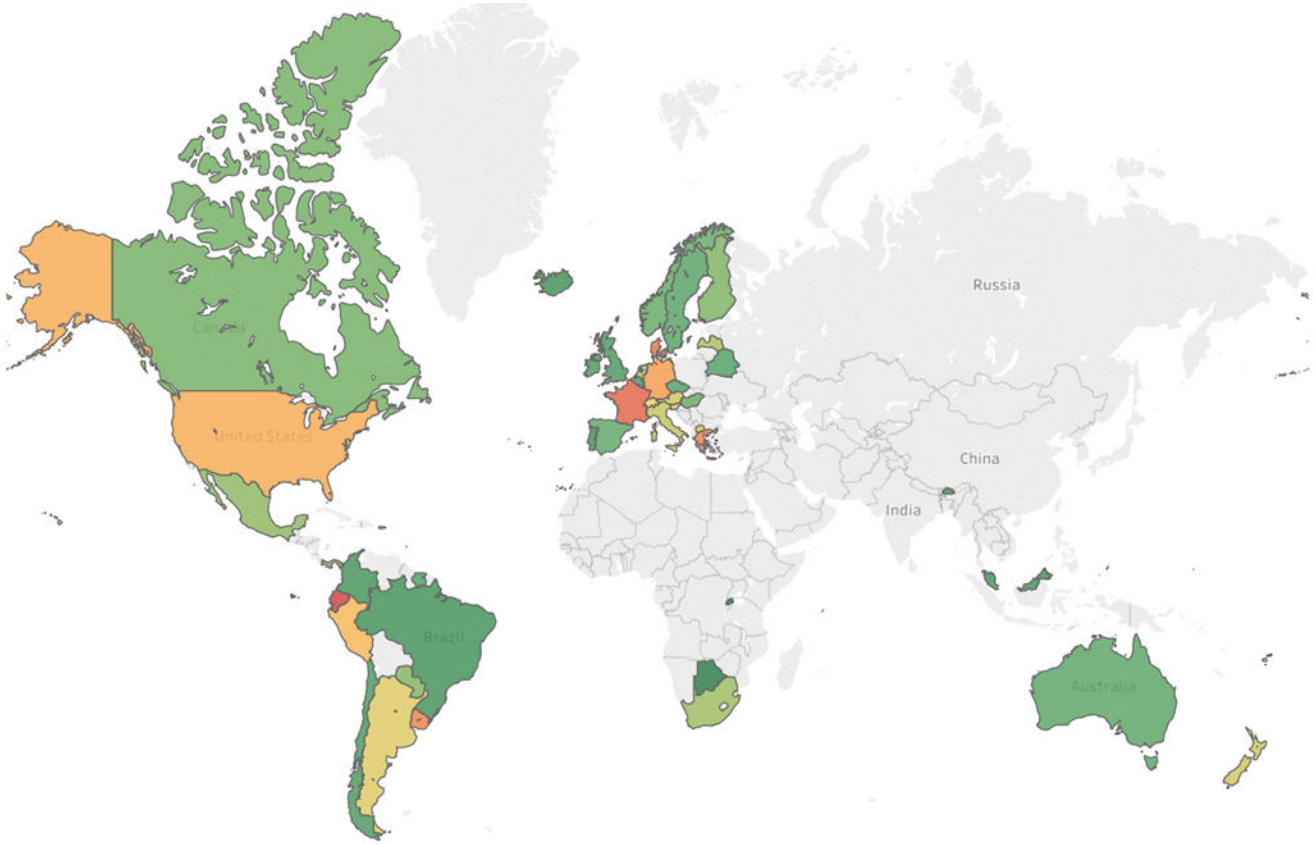


Figure 4.

Full-course human papillomavirus vaccination coverage (2009–2017). Note: Coverage is defined as the proportion of the targeted population receiving full-course (two or three doses) human papillomavirus vaccination. Red/orange shades indicate coverage of approximately 0%–45% (darker indicating lower), lighter green shades indicate coverage of approximately 50%–70%, and darker green shades indicate coverage above approximately 70%, darkest shades indicating highest coverage). An interactive version of this map is available (https://public.tableau.com/views/HPVVaccineReviewV3_0/NationalandDemoProgramsalltime2?:embed=y&:useGuest=true&:display_count=yes).

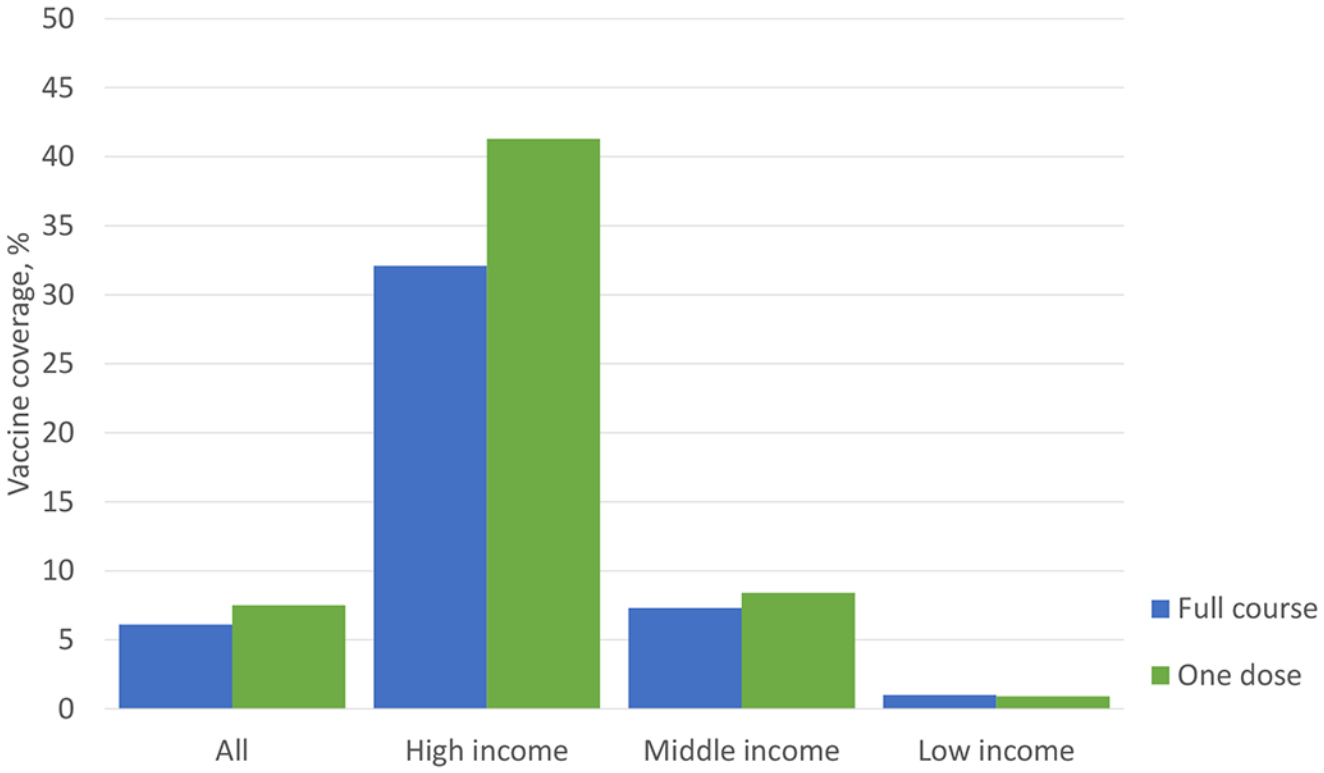


Figure 5.

Proportion of 10–20-year-old girls receiving human papillomavirus vaccination by country income group. The World Bank defines the income groups by gross national income per capita as: low income, US$1,005 or less; lower middle income, US$1,006–3,955; upper middle income, US$3,956–12 235; and high income, US$12 236 or more. Adapted from Bruni L et al. [16].

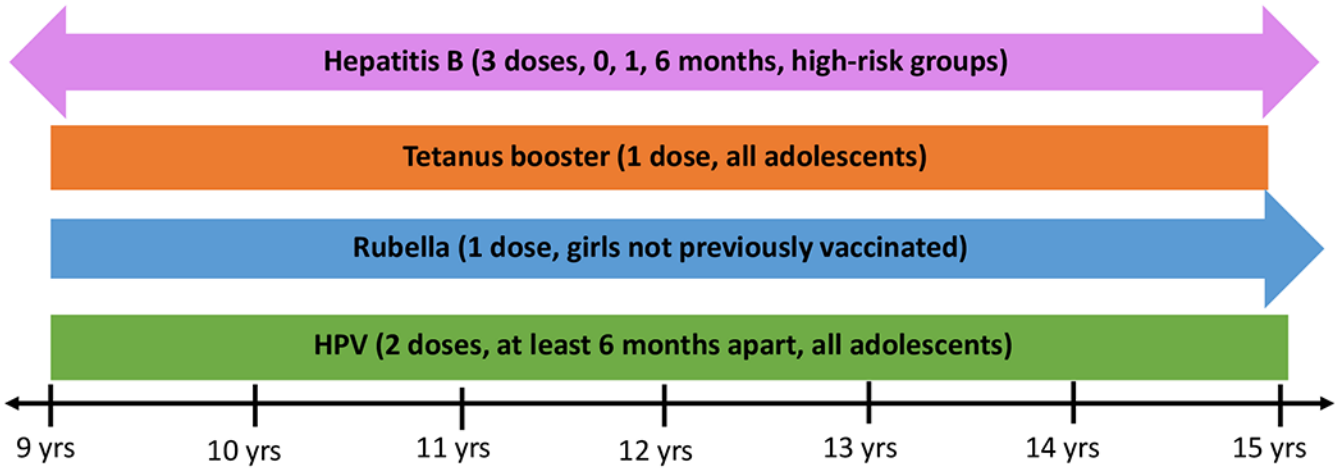


Figure 6.
Vaccination schedule for adolescents aged 9–15 years as recommended by the WHO.

Table 1

Efficacy of currently approved prophylactic HPV vaccines.

Characteristic	Bivalent [3]	Quadrivalent [4]	Nonavalent [5]
HPV types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Adjuvant	AS04	AAHS	AAHS
Efficacy [a]			
HPV-naïve women			
Vaccine-type HPV infection	93 (89–95)	81 (68–89)	96 (94–98)
CIN2+ associated with HPV-16/18	95 (88–98)	98 (94–100)	ND
CIN2+ associated with HPV-31/33/45/52/58	NA	NA	96 (80–100)
CIN2+ associated with any HPV type	65 (53–74)	43 (24–57)	ND
All women			
CIN2+ associated with HPV-16/18	61 (50–70)	52 (41–61)	ND
CIN2+ associated with any HPV type	33 (22–43)	18 (7–28)	ND

Abbreviations: AAHS, amorphous aluminum hydroxyphosphate sulfate; AS04, 3-O-desacyl-4′-monophosphoryl lipid A adsorbed on aluminum (as hydroxide salt); CIN, cervical intraepithelial neoplasia; NA, not applicable, ND, no data.

[a]Values are given as percentage (95% confidence interval).

Table 2

Selected epidemiologic models estimating the impact of HPV vaccination.

Source	Population	Vaccine	Assumptions	Primary results [a]
Jit et al. 2014 [16] (PRIME)	12-year-old girls; 179 countries	2vHPV; no cross-protection	100% efficacy; lifelong protection; 100% coverage; no herd immunity; no dynamic transmission; screen/treat not included	690 000 cases and 420 000 deaths over the lifetime of the cohort
Van Kriekinge et al. 2014 [17]	Young girls naïve to HPV; 175 countries	2vHPV; cross-protection	93% efficacy; lifelong protection coverage varies; no herd immunity; no dynamic transmission; screen/treat not included	50% coverage: 246 000 cases/year; 127 000 deaths/year
				90% coverage: 443 000 cases/year; 229 000 deaths/year
Goldie et al. 2008 [18]	9-year-old girls; 72 Gavi-eligible countries	2vHPV; no cross-protection	100% efficacy; lifelong protection; 70% coverage; no herd immunity; no dynamic transmission; screen/treat not included	3 million deaths over the lifetime of 10 consecutive birth cohorts
Kim et al. 2013 [19]	12-year-old girls; 48 Sub-Saharan African countries	2vHPV; no cross-protection	100% efficacy; lifelong protection; 70% coverage; no herd immunity; no dynamic transmission; screen/treat not included	670 000 cases over the lifetime of five consecutive birth cohorts
Van de Velde et al. 2012 [20]	12-year-old girls; Canada	2v-, 4v-, 9vHPV; cross-protection	100% efficacy; lifelong protection; 70% coverage; includes herd immunity; dynamic transmission; screen/treat included	CIN2/3 reduction over 70 y: 2vHPV, 51%; 4vHPV, 46%; 9vHPV, 60%

Abbreviations: 2vHPV, bivalent vaccine; 4vHPV, quadrivalent vaccine; 9vHPV, nonavalent vaccine; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

[a] Number of cases/deaths prevented unless indicated otherwise.