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Human papillomavirus vaccine disease impact beyond expectations

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Since 2006, 115 countries and territories have introduced human papillomavirus (HPV) vaccination programs.

Several efforts have been undertaken to evaluate the impact of HPV vaccines. Many countries, mainly high-income and with high screening coverage, are already reporting a visible impact of the HPV vaccine on HPV-related diseases. Others, largely low-income and middle-income countries, are introducing HPV vaccine to control HPV diseases that will undoubtedly generate a similar impact.

In this review, we will summarize the compelling evidence of the impact of vaccines in reducing the burden of HPV-related disease. The data support additional efforts to make HPV vaccines widely available to adolescent girls in the countries that bear the vast majority of cervical cancer-related morbidity and mortality.

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Introduction

Human papillomavirus (HPV) belong to the Papillomaviridae family, which includes more than 200 different genotypes with different tropism and pathogenesis [1]. Mucosal HPV types are commonly classified as low and high risk according to their capacity to induce cancer [2••]. Carcinogenic HPV types include HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV52, HPV56, HPV51, HPV58, and HPV59. Two additional types, HPV68 and HPV66, although often included as high-risk types, have a questionable capacity to induce cancer. Although varying in their contribution in cancer, oncogenic types have been linked to cervix, anal, vulva, vagina, penile, and oropharynx cancer sites [3,4]. Worldwide, HPV infection still causes up to 4.5% (630 000 cases) of all new cancer cases worldwide (8.6% in females; 0.9% in males), representing 29.5% of all infection-related cancers [4,5••]. The low-risk types HPV6 and HPV11 cause genital warts that are among the most common sexually transmitted diseases. HPV6 and HPV11 also cause recurrent respiratory papillomatosis (RRP), a proliferative and rare disease of the upper aero-digestive tract acquired during vaginal delivery affecting children and young adults that can cause serious morbidity [6,7].

Prophylactic HPV vaccines have been progressively introduced worldwide since 2006. Large phase III randomized clinical trials and post-licensure studies and trials have proven high efficacy, effectiveness, and safety records in the prevention of vaccine-type HPV infection and cancer precursor lesions (cervical intraepithelial neoplasia [CIN1-3]) [8,9,10•,11•], Currently, three HPV vaccines are commercially available (bivalent, quadrivalent, and nonavalent). All three contain virus-like particles (VLPs) of HPVs 16/18. The quadrivalent and nonavalent vaccines also contain VLPs from HPVs 6/11. The nonavalent vaccine additionally protects against HPVs 31/33/45/52/58 [12]. The bivalent vaccine has demonstrated a high degree of cross-protection against types 31, 35, and 45 with an overall efficacy against all CIN3, irrespective of the HPV type, of 93% [10•]. This cross-protection has been recently corroborated in observational studies from Scotland [13]. The quadrivalent vaccine has established more restricted cross-protection, most notable against type 31 [14]. From a public health perspective, the three vaccines offer comparable immunogenicity, efficacy, and effectiveness for the prevention of cervical cancer, mainly caused by HPV16 and HPV18 [15]. In accordance with the genotype attribution to different cancer sites, the existing vaccines could prevent up to 90% of HPV-associated cancers [3,16,17] and related pre-neoplastic lesions.

HPV vaccine global implementation

On the basis of a thorough and sustained review of official announcements at the national level and on the data on vaccination schedules maintained by the World Health

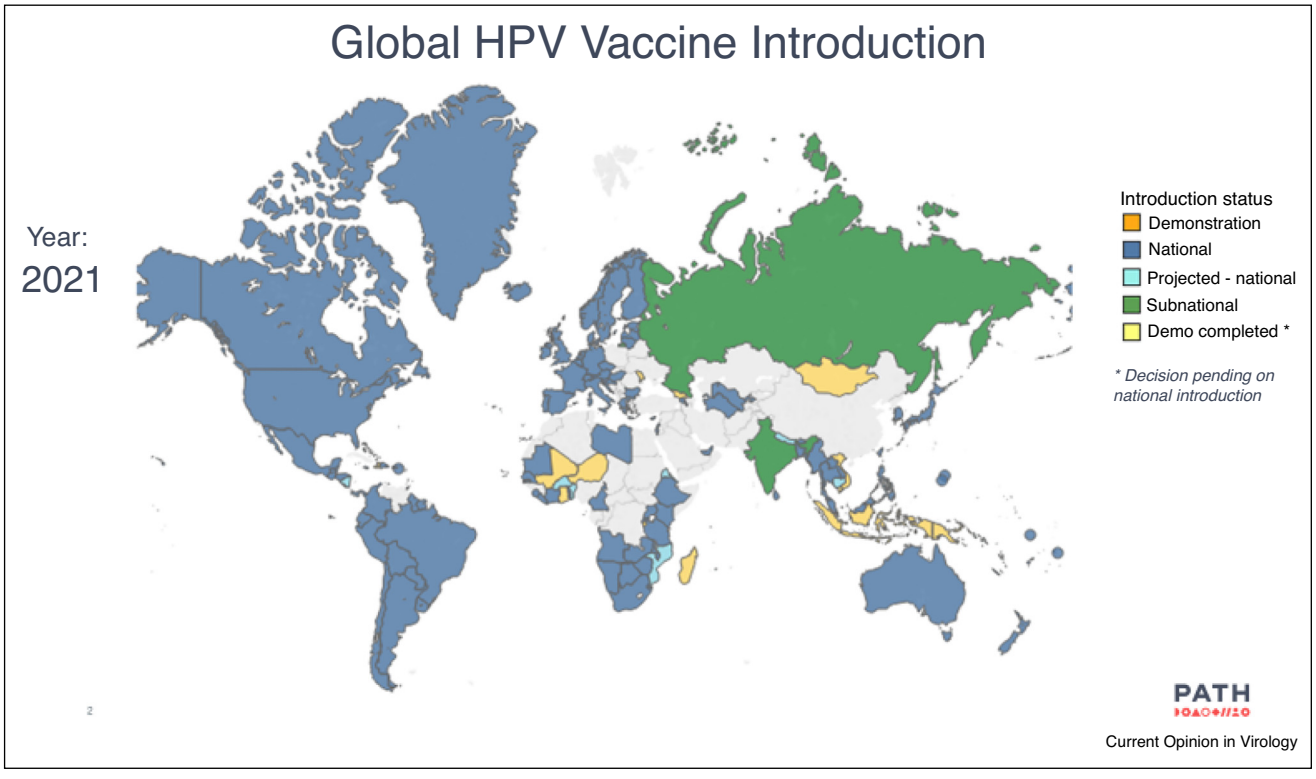
Organization (WHO) and previously published reports [18•,19], as of early 2019, 115 countries and territories (95 are WHO Member States) have introduced HPV vaccine into their national schedule and, among these, 20 countries and 4 territories have gender-neutral HPV vaccination schedules. Globally, 52 countries have conducted pilots or demonstration projects to gain operational experience to inform decision-making for national introduction. Provided sufficient vaccine supply, an additional 39 countries and territories are projected to have HPV vaccine on their national schedule by the end of 2021, and 26 countries have received Gavi, the Vaccine Alliance (Gavi) approval for the introduction of HPV vaccines. Figure 1 depicts the projected countries that will have a national vaccination program by 2021. To monitor the extent to which national programs are reaching the target population for HPV vaccines, regular compilations of available data are undertaken, involving several global teams, such as WHO, PAHO, PATH, Gavi, and ICO. The most recent data publicly available with the estimated countries that will have introduced by 2021 HPV vaccine are shown in Figure 1.

HPV vaccine impact

HPV type-specific prevalence, diagnosis of new genital infection, precursor cancer lesions, cancer sites associated with HPV, anogenital warts, and RRP are all potential outcomes to evaluate changes induced by HPV vaccination. HPV infections are mostly being monitored by HPV-prevalence surveys or through the analysis of residual specimens from women attending either cervical or chlamydia screening. Both HPV type-specific prevalence (an incidence surrogate) and incident cases of genital warts (an early disease outcome) are used in most high-income countries to monitor the early impact of vaccination.

To evaluate the effectiveness of a vaccine, changes in the prevalence of infection and disease outcomes need to be measured in vaccinated versus unvaccinated populations, with the requirement of individual data on HPV-vaccination status. Measuring the population impact of a vaccination program involves the amount of changes over time of a given outcome in the population, irrespective of the individual vaccine status (before and after study or time-trend analysis). More than 100 studies have been published to date showing major effectiveness and impact on HPV infection and disease outcomes. A recent and robust meta-analysis presented by Drolet *et al.* [20••] provides the most updated data on the evaluation of HPV-vaccine impact. A summary of the HPV vaccine population impact is presented in Table 1.

Figure 1



Global HPV vaccine introduction by 2021.
(Slide courtesy of PATH, D. Scott LaMontagne, June 2019)

Table 1

Summary of HPV vaccine impact by outcomes as publicly reported by 2019

Endpoint	Population	Main findings	Reference
HPV 16–18 prevalence	Girls aged 13–19y	83% decrease after 5–8 years of vaccination[a] (RR 0.17 [95% CI 0.11–0.25])	Drolet *et al.* [20••]
	Women aged 20–24y	66% decrease after 5–8 years of vaccination[a] (RR 0.34 [95% CI 0.23–0.49])	
	Women aged 25–29y	37% decrease after 5–8 years of vaccination[a] (RR 0.63 [95% CI 0.41–0.97]).	
	Boys aged 16–19y	Non-significant decrease of 65% after 4 years of female vaccination[a] (RR 0.35 [95% CI 0.09–1.40])	
HPV 31, 33, 45 prevalence	Girls aged 13–19y	54% decrease after 5–8 years of vaccination[a] (RR 0.46 [95% CI 0.33–0.66])	Drolet *et al.* [20••]
	Women aged 20–24y	Non-significant decrease of 28% after 5–8 years of vaccination[a] (RR 0.72 [95% CI 0.47–1.10])	
	Boys aged 16–19y	Non-significant decrease of 69% after 4 years of female vaccination[a] (RR 0.31 [95% CI 0.06–1.58])	
Genital warts	Girls aged 15–19y	67% decrease after 5–8 years of vaccination[a] (RR 0.33 [95% CI 0.24–0.46])	Drolet *et al.* [20••]
	Women aged 20–24y	54% decrease after 5–8 years of vaccination[a] (RR 0.46 [95% CI 0.36–0.60])	
	Women aged 25–29y	31% decrease after 5–8 years of vaccination[a] (RR 0.69 [95% CI 0.53–0.89])	
	Boys aged 15–19y	48% decrease after 5–8 years of female vaccination[a] (RR 0.52 [95% CI 0.37–0.75])	
	Men aged 20–24y	32% decrease after 5–8 years of female vaccination[a] (RR 0.68 [95% CI 0.47–0.98])	
CIN2+	Screened girls aged 15–19y	51% decrease after 5–9 years of female vaccination[a] (RR 0.49 [95% CI 0.42–0.58])	Drolet *et al.* [20••]
	Screened women aged 20–24y	31% decrease after 5–9 years of female vaccination[a] (RR 0.69 [95% CI 0.57–0.84])	
Juvenile-onset RRP	Girls and boys aged <15y	Decrease in incidence rates from 0.16 per 100.000 in 2012 to 0.02 in 2016. No cases were identified in 2018	Teutch *et al.* [30] Novakovik *et al.* [32] Nunez *et al.* [31] Brotherton, personal communication

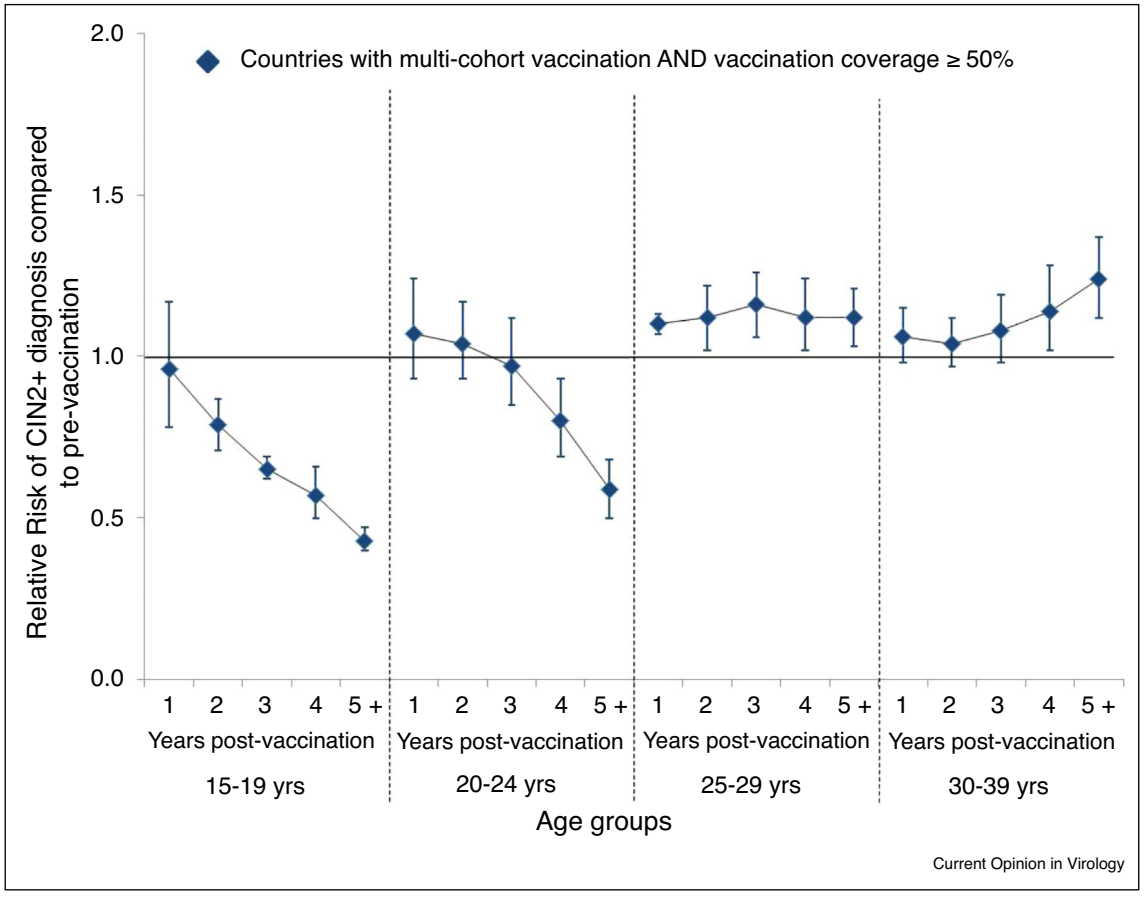
Abbreviations: HPV, human papillomavirus; y, year; RR, risk ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; RRP, recurrent respiratory papillomatosis.
[a] Compared to the pre-vaccination period.

The Drolet *et al.* meta-analysis includes 65 studies from 14 high-income countries, and pools individual data from over 60 million individuals for up to eight years of post-vaccination follow-up. All studies were conducted in the context of three-dose HPV vaccine recommendations and programs. The data exclude randomized clinical trials or studies with no data before vaccination. The report shows overall significant reductions of 80% on the prevalence of types HPV16 and HPV18, a reduction of 70% in anogenital wart diagnoses, and a significant reduction in CIN2+ pre-cancerous lesions. An additional and statistically significant 54% reduction of the prevalence of non-vaccine types HPV31/33/45 was observed for women aged 13–19 years. Genital warts were reduced by 67% in women aged 15–19 years and by 31% among women aged 25–29 years. Further, a considerably higher impact in genital warts was also observed on settings where a multi-age cohort vaccination reached vaccine coverage of 50% or more. A significant reduction in genital warts was also observed in males up to age 29 years old when multiple cohorts with a coverage over 50% was reached. Girls aged 15–19 years old and women aged 20–24 years old had a 51% and 31% reduction in CIN2+ detection, respectively, 5–9 years after HPV vaccination. To better understand the magnitude of the changes, Figure 2 illustrates the detection of CIN2+ in the vaccination years as compared to the detection of CIN2+ in the pre-vaccine era. The impact on CIN2+ reduction is clearly observed in the younger cohorts but not in women aged 25 years or older.

A major observation of the overall data reported by Drolet *et al.* is that faster, higher-impact, and herd effects were observed in countries vaccinating multiple age cohorts that achieved high coverage compared with single cohort vaccination and/or low coverage.

In line with these observations, Palmer *et al.* [13] reported data from Scotland where vaccination and screening records of nine birth cohorts of 20-year-old women were extracted to evaluate the effectiveness of the bivalent HPV vaccine at preventing cervical precancerous lesions

Figure 2



Changes in CIN2+ among screened girls/women between the pre-vaccination and post-vaccination period [20••].

diagnosed at a woman's first cervical screening episode. The analysis identified an 89% reduction of prevalent CIN3+; an 88% reduction of CIN2+; and a 79% reduction of CIN1 in vaccinated women born in 1995 and 1996 compared with unvaccinated women born in 1988.

Unvaccinated women also showed lower prevalence of CIN3+ lesions, supporting a herd protection effect by which, through vaccination, a reduction in HPV16/18 infections would have not only an impact on the women themselves but also on the overall network of male–female sexual relations.

The fact that the vaccination program reduced all type of CIN3+ lesions, and not only those related to HPV16 or HPV18 (the types included in bivalent vaccine), indicated a strong cross-protection on common oncogenic types like HPV31/33/45, as supported by previous clinical trial data [21,22].

Markowitz *et al.* [23] reviewed vaccine effectiveness, by number of doses, of studies published until 2017. In this review, three studies found significant effectiveness of one dose against genital warts, one study on HPV prevalence, and two studies on high-grade cervical lesions, although only in some age groups and with increasing buffer periods.

Further, there is a recently published paper analyzing national data from Denmark showing statistically significant effectiveness of one dose against CIN3+ [24]. However, data to document a vaccine impact on pre-neoplastic or neoplastic disease using reduced regimes are still limited and need to be evaluated with caution. Palmer *et al.* did not find a significant reduction on cervical lesions in those receiving only one dose, but numbers were very limited. Several randomized controlled trials are ongoing to evaluate the efficacy of a one-dose regimen.

The impact of HPV vaccines on invasive cervical cancer at the population level will need several more years to be fully visible. Preliminary data are available from the follow-up of cancer registries of Finnish women vaccinated in the HPV-vaccine clinical trials. Luostarinen *et al.* linked data from vaccination trial cohorts and compared to non-vaccinated cohorts, with data from the national cancer registry for the

period 2002/2007–2015 [25]. A significant risk difference of $-6.4/10^5$ (95% CI: $10.9/10^5$ to $-2.0/10^5$, $p = 0.0169$) was observed. No single cancer case was diagnosed in the vaccinated cohort, versus eight cases of cervical cancer, one vulvar cancer, and one oropharyngeal cancer in the non-vaccinated cohort [25]. However, in this analysis vaccinated and non-vaccinated cohorts were not comparable, limiting the interpretation of the data.

The study of the annual incidence of invasive cervical cancer in the USA in the four years before the introduction of HPV vaccine (2003–2006) was compared to the incidence of cervical cancer in the vaccine era (2011–2014). A significant reduction of 29% in the four-year average annual incidence rates was observed during the study period (6.0 versus 8.4 per 1 000 000 people, rate ratio = 0.71, 95% CI: 0.64–0.80) among females aged 15–24 years, and 13.0% lower among females aged 25–34 years [26]. During these years, the vaccine coverage increased up to 55.3% in the younger cohorts. Data are suggestive that a strong downtrend could be attributed in part to the vaccine introduction, although incidence rates were already decreasing before the vaccine was introduced. Changes in screening practices make these decreases difficult to interpret.

Effectiveness on HPV oral infection

Data on the impact on oral HPV infection by HPV vaccines at this site are not yet available. There are two published studies analyzing the effectiveness on oral HPV infection from the United States National Health and Nutrition Examination Survey (NHANES). Hirth *et al.* reported a reduced prevalence of oral HPV6/11/16/18 infections in vaccinated individuals compared to non-vaccinated individuals (1.99% versus 3.52%, $p = 0.04$) [27]. Further Chaturvedi *et al.*, using the NHANES surveys from 2011 to 2014, where 29.2% women and 6.9% men reported receipt of at least one dose of the HPV vaccine, also identified a significantly lower prevalence of oral HPV6/11/16/18 infections in vaccinated individuals than in non-vaccinated individuals (0.11% versus 1.61%; $p = 0.008$), with an estimated 88.2% reduction (95% CI: 5.7% to 98.5%) in oral HPV6/11/16/18 prevalence, adjusting for age, sex, and race [28]. HPV16 prevalence was non-significantly lower in vaccinated than in non-vaccinated individuals (0.11% versus 0.94%, $p = .063$). Further, Mehanna *et al.* evaluated the oropharyngeal HPV infection in subjects undergoing tonsillectomy in six hospital in the United Kingdom and identified that oropharyngeal HPV16 prevalence in vaccinated girls was significantly lower than in unvaccinated girls (0.5% versus 5.6%, $p = 0.04$), with similar prevalence of any HPV type (19% versus 20%, $p = 0.76$) [29].

Impact on HPV-related rarer outcomes

As mentioned before, RRP is a rare disease that can affect children and young adults and often require multiple surgical procedures, sometimes with a fatal result. Active surveillance of pediatric reports in Australia has allowed observation of a continuous decrease, from 2012 to 2018, of the incidence of the juvenile form of RRP with rates of 0.16 per 100 000 in 2012 to 0.02 per 100 000 in 2016 and to zero cases in 2018 [30,31,32 and Julia Brotherton personal communication]. This continuous decrease occurred in parallel to the wide coverage of HPV vaccination in the Australian population, suggesting an important reduction of intrapartum HPV transmission from mothers to infants.

Anal cancer has been increasing in many countries in recent years. Still, this is a rare cancer in the general population, although more frequent in some subgroups like men who have sex with men (MSM) or the HIV-infected population, the majority of which have had little chances to be vaccinated before HPV exposure. Any impact of the HPV vaccines on anal cancer may require a longer observational period. Similarly, vulvar cancer and cancer of the penis are rare cancers with generally a later onset as compared to cervical cancer. Any measurable impact in these cases will take decades.

Challenges of monitoring the impact of HPV vaccines

Since the introduction of HPV vaccines, there has been an increasing body of evidence regarding the population impact and the effectiveness of HPV vaccines in the reduction of prevalence of high-risk types, and the incidence of anogenital warts and high-grade cervical lesions, as discussed above. These data are consistent across different regions and, to date, there is no evidence that HPV vaccines will work differently in particular regions. Monitoring HPV-related outcomes is not a prerequisite to introduction of HPV-vaccination programs, according to the WHO [11], but in some settings, confirming the impact on local populations could help maintain the sustainability of the program. Nevertheless, there are several aspects that need to be considered when vaccine-impact evaluations are required: the long latency period between HPV infection and development of HPV-related cancers; multiple disease outcomes that develop at different times after infection and are diagnosed in different settings and through different methods; necessity of coordination between different programs (immunization, sexually transmitted diseases, adolescent health, cancer prevention or cancer registries); coexistence of screening programs, that will directly determine the burden of cervical precancerous lesions and will affect the incidence and mortality of cervical cancer; the scarcity of surveillance systems or registries for HPV-related outcomes and lack of individual data on vaccination status [33,34]. Whether or not there are other monitoring activities, all countries should consider establishing or improving the reporting of cervical cancer to population-based cancer registries [11]. As impact evaluation is complex and presents a number of challenges, all countries should prioritize increasing HPV-vaccine uptake and establishing information systems to assure monitoring of

HPV vaccination uptake, irrespective of whether they can assess the impact of the HPV vaccine.

Those countries that are planning to assess the impact of HPV vaccines could consider the following items to establish which outcomes to monitor: time-to-impact evaluation (short-term evaluation on HPV prevalence or genital warts, medium-term evaluation on cervical precancerous lesions, and long-term evaluation on cervical cancer); available infrastructure (laboratory, personnel, health information system, vaccination and cancer registries, etc.); potential sources of information available (cancer registries, cervical cancer screening registries, immunization registries, administrative data from sexually transmitted infections clinic, electronic health records, etc.); possible recruitment strategies; capacity to maintain monitoring over time and budgetary impact of the different options.

Conclusion

HPV vaccines have been proven to work extremely well, resulting in an impact far beyond initial expectations. Results show that when more than half of the female population is vaccinated, the burden of HPV infection, related precancerous lesions, and genital warts can significantly decrease, potentially leading to elimination. Herd effects expand to unvaccinated heterosexual males, resulting in significant reductions of disease for them as well.

Importantly, this evidence on the impact of vaccines is compelling and thoroughly consistent across settings. One outstanding implication is that at similar levels of vaccine coverage, impact is expected to be not inferior to the one already observed worldwide. With current evidence, there is no need to repeatedly ascertain these same results for all established HPV immunization programs.

The main priority of countries should be first, to introduce the vaccine in their national schedules if they have not, and second, to achieve and maintain high coverage rates. In closing, WHO has opened for public discussion their proposed strategy to eliminate cervical cancer in this century to a level of less than four new cervical cancer cases per 100 000 women [35••]. In addition to screening interventions, the strategy proposes that 90% of all girls worldwide should be vaccinated by age 15. This strategy will result in millions of girls free from HPV-related disease for the rest of their lives and, as seen in the data presented, high vaccination coverage in adolescent girls also will protect their male partners. Monitoring progress at different levels according to each country's capacity is fundamental to pave the way towards the elimination goal.

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- •• of outstanding interest

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