Human papillomavirus vaccination and cervical cancer risk

Lisa Rahangdale,[1,2,3] Chemtai Mungo,[1,2,3] Siobhan O'Connor,[4] Carla J Chibwesha,[1,5] Noel T Brewer[2,6]

[1]Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[3]Center for AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[4]Department of Pathology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[5]Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa
[6]Department of Health Behavior, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Correspondence to:
L Rahangdale
lisa_rahangdale@med.unc.edu

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Abstract

Persistent human papillomavirus infection is the central cause of cervical cancer, the leading cause of cancer death among women worldwide. Clear evidence from both randomized trials and population based studies shows that vaccination against human papillomavirus reduces the incidence of cervical pre-cancer. These data suggest that the vaccine reduces the incidence of cervical cancer. However, human papillomavirus vaccine coverage is inadequate in all countries, especially in low and middle income countries where disease burden is highest. Supply side strategies to improve coverage include increasing the availability of low cost vaccines, school located delivery, single dose vaccine schedules, and development of vaccines that do not need refrigeration. Demand side strategies include enhancing provider recommendations, correcting misinformation, and public awareness campaigns. The near elimination of cervical cancer is achievable through increased uptake of human papillomavirus vaccination and efforts to increase screening for cervical cancer, especially when enacted to reduce disparities in across the world.

Introduction

The progression of cervical cancer is well characterized (fig 1).[1 2] High risk human papillomavirus (hrHPV) infects metaplastic cells at the cervical transformation zone and integrates into the host genome,[3] leading to inactivation of the tumor suppressor genes *p53* and *Rb*, cell proliferation, and accumulation of mutations.[4] Genetic predisposition, hormonal factors, host immune response, and cigarette smoking increase susceptibility to hrHPV infection.[3] As persistent human papillomavirus infection is the central cause of invasive cervical squamous cell carcinoma (ICC),[5] and pre-cancerous lesions are generally detectable, prevention of cervical cancer relies primarily on preventing infection through human papillomavirus vaccination (primary prevention) and detecting and treating pre-cancerous lesions (also known as high grade cervical intraepithelial neoplasia (CIN2/3) or adenocarcinoma in situ (ACIS)) before they progress to cancer (secondary prevention).

The first human papillomavirus vaccine was introduced into clinical care in 2006.[6] Bivalent (human papillomavirus 16/18), quadrivalent (human papillomavirus 6/11/16/18), and nonavalent (human papillomavirus 6/11/16/18/31/33/45/52/58) vaccines are prequalified by the World Health Organization and widely licensed.[7] All available vaccines provide protection against human papillomavirus 16 and 18, as approximately 70% of cervical cancers worldwide are attributable to these two virus types[5]; the nonavalent vaccine prevents subtypes that account for an additional 19%.[8]

WHO set a target for 194 countries to adopt human papillomavirus vaccination by 2030 in its *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*.[9] By 2020, however, only 114 countries had introduced human papillomavirus vaccines; most of these are high income countries.[10] Less than 25% of low income countries have human papillomavirus vaccination as part of their national immunization schedules. Most gaps in the introduction and coverage of human papillomavirus vaccine are in regions of Africa and Asia where the burden of cervical cancer is also high.[10]

Global efforts to nearly eliminate cervical cancer focus on expanding access to human papillomavirus vaccination and cervical cancer screening.[9] In this article, we summarize clinical data on the efficacy and effectiveness of human papillomavirus vaccination, its potential impact on incidence of ICC, and strategies to increase access to and uptake of vaccination for general practitioners and specialists in positions to offer human papillomavirus vaccination to individual patients and/or affect policy.

Sources and selection criteria

We developed the tables to illustrate the evidence on the impact of human papillomavirus vaccination on cervical pre-cancer and, potentially, cervical

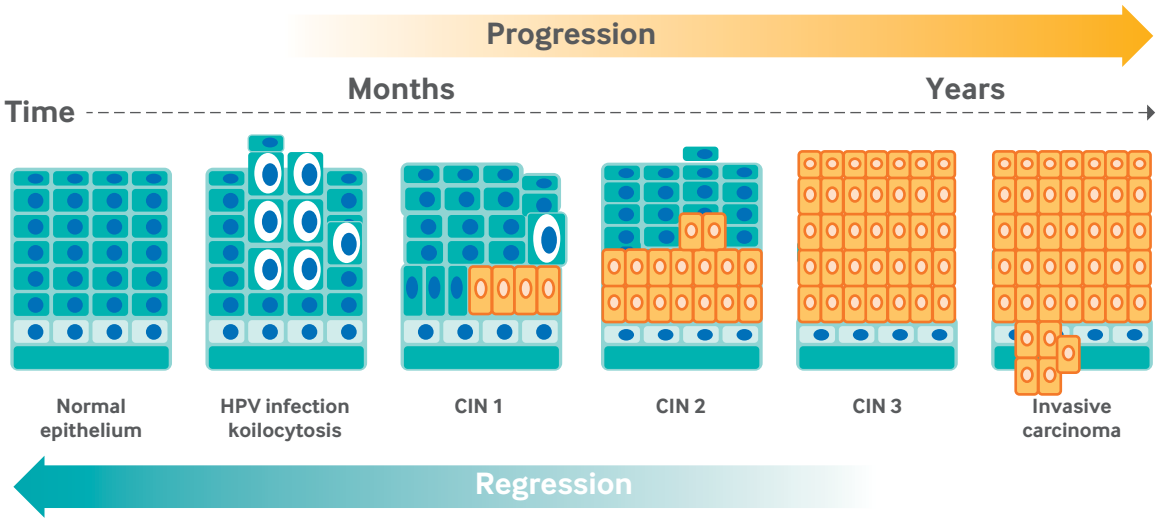

Fig 1 | Progression of cervical disease after human papillomavirus infection. CIN=cervical intraepithelial neoplasia. Adapted from references 1 and 2

cancer. We searched PubMed, Embase, and CINHAL by using the following predefined terms: (HPV OR human papillomavirus OR human papilloma virus) AND (vaccine OR vaccines OR immunization OR immunisation OR shot) AND (CIN OR cervical intraepithelial neoplasia) AND (impact OR effect OR effectiveness). After the initial search, we selected the "randomized controlled trial" filter under "article type" on PubMed. We also searched lists of references and lists of studies that had cited the specific study, linking to studies published on PubMed or Embase. The literature search for the tables was completed on 16 May 2022 and included studies up to this date. Quality criteria used to select papers for the tables included randomized control trials and population based cohort (registries or databases) studies in which both human papillomavirus vaccination and pathologic diagnosis were documented in the dataset. We did not include studies based on self-report of vaccination or having hrHPV infection as the only endpoint. Additionally, we prioritized the most recent national and international recommendations on human papillomavirus vaccination for inclusion in the human papillomavirus vaccination guidelines and recommendations section.

Epidemiology

Cervical cancer is the fourth most common cancer among women and other people with a cervix worldwide, with a global incidence of 13.3 per 100 000 in 2020.[11] Eight of every 10 cases of ICC occur in low and middle income countries (LMICs)—a disparity driven by inequity in access to prevention and treatment of cancer.[12 13] Africa has an estimated 20% of the world's ICC, about 120 000 cases per year. More specifically, ICC is the leading cause of death from cancer among women in sub-Saharan Africa,[14 15] which is also the global epicenter of the HIV pandemic.[16] More than 11 million women living with HIV are in sub-Saharan Africa. In addition to many barriers in access to human papillomavirus vaccination and cervical screening, these women face a substantially higher risk of persistent hrHPV infection.[17-19] Women living with HIV are also more likely to be diagnosed as having cervical cancer or cervical pre-cancer.[20]

Incidence of ICC in high income countries has decreased over the past three decades but remains an important public health concern.[21] Europe is a high income region where an estimated 58 169 women annually are found to have ICC (10.7 per 100 000 women) and 25 989 women die from ICC.[22] By contrast, Australia will have an estimated 942 new diagnoses of ICC (7.1 per 100 000 women) and 222 deaths in 2022.[23] Figure 2 illustrates risks worldwide in relation to a high income country such as the United States.[24 25] The US had 12 795 new cases of ICC (7.5 per 100 000 women)[26] and 4152 deaths in 2019. The numbers have been falling in the past several decades, largely owing to screening for cervical cancer.[27] However, serial national cross sectional household surveys indicate that guideline concordant rates of screening went down between 2005 and 2019 in the US.[28] This drop is likely more significant than reported owing to the tendency to over-report screening in self-report studies,[29] as well as the subsequent covid-19 pandemic.

The incidence of ICC in Asia (12.7 per 100 000)[30] was lower than in Africa (24.6 per 100 000)[31] but nearly twice that in Europe and the US in 2020. An upward trend in cases is noted in both sub-Saharan Africa and east Asia.[21] The incidence in Latin America and the Caribbean was estimated at 14.9 per 100 000 women in 2020.[32] Disproportionately higher incidence and mortality occurs in Latin America and the Caribbean, with mortality rates three times higher than in North America and accounting for 89% of ICC deaths in the Americas.[33]

Impact of human papillomavirus on risk of cervical cancer

Extensive evidence supports the safety and efficacy of human papillomavirus vaccination for prevention of precursors of ICC. A Cochrane review included 26

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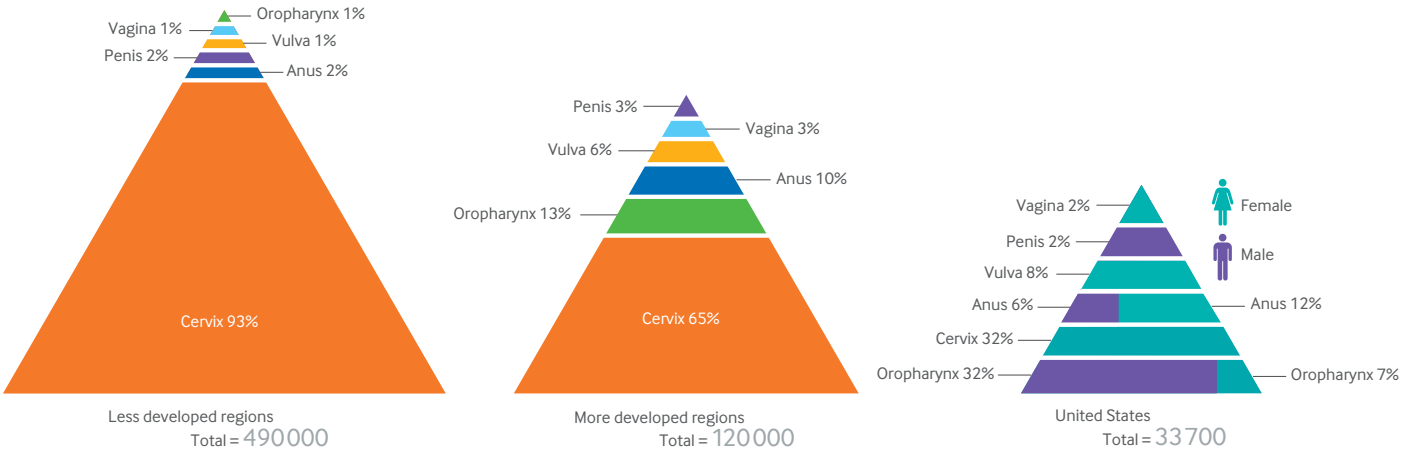

Fig 2 | Numbers of human papillomavirus associated cancers. Adapted from references 21 and 22

trials (73 428 participants), of which 10 concluded that human papillomavirus vaccination leads to prevention of cervical pre-cancer, particularly in adolescent girls and women who were negative for human papillomavirus before vaccination.[34] A systematic review and meta-analysis with data for more than 60 million people found that the risk of CIN2+ decreased by 51% (relative risk 0.49, 95% confidence interval 0.42 to 0.58) among 15-19 year old female patients vaccinated against human papillomavirus and by 31% (0.69, 0.57 to 0.84) among vaccinated 20-24 year olds.[35] Table 1 includes multiple randomized clinical trials that were designed to show safety and hrHPV 16/18 genotype specific efficacy for reduction of cervical pre-cancer (CIN2+) after bivalent, quadrivalent, and nonavalent human papillomavirus vaccination.[36-40] Table 2 shows data from multiple population based observational studies using national registries or databases. Vaccine effectiveness for CIN2+ has been demonstrated with one, two, and three doses of vaccine.[41-49]

Given these positive results, interest is increasing in how vaccination programs may reduce the incidence of ICC through herd immunity and achieve the near elimination of cervical cancer. Australia's national human papillomavirus vaccination program started in 2007 for girls aged 12-13 and in 2013 for boys the same age, with catch-up to age 26. A review of epidemiologic studies in Australia found a decline in the national incidence of CIN2+/ACIS in women up to age 29.[50] The authors estimated that 72% of cervical cancers would be prevented by quadrivalent human papillomavirus vaccine and an additional 15% prevented by the introduction of the nonavalent vaccine. Australia's prevention program of vaccination and screening is on track to lower ICC incidence to below four per 100 000 women by 2035, making the country the first to nearly eliminate cervical cancer.[51]

Data from 2006 to 2017 from Sweden's national human papillomavirus vaccination program in girls and women aged 10-30 years were used to assess for risk of ICC, specifically. In a female population of more than 1.6 million, Sweden had 538 cases of ICC in the unvaccinated population compared with 19 cases in the vaccinated (at least one dose) population. The adjusted incidence rate ratio was 0.12 (95% confidence interval 0.00 to 0.34) and 0.47 (0.27 to 0.75) for those vaccinated before age 17 or between 17 and 30 years, respectively.[52]

A modeling study examined the effect of England's national human papillomavirus vaccination program that started in 2008 in 12-13 year old girls with catch-up to 18 years. It showed a risk reduction of 97% (95% confidence interval 96% to 98%) for CIN3 and 34% (25% to 41%) for cancer in the cohort vaccinated at ages 12-13 years. A reduction in risk was also seen in those vaccinated in the catch-up group of up to 18 years.[53] Outcomes were based on data from 20-30 year old women, a population with low rates of cervical cancer.

Japan's initial human papillomavirus vaccination program for 12-16 year old girls started in 2010 and showed a decline in human papillomavirus 16/18 CIN2-3/ACIS from 48% to 33%, especially in women first vaccinated before age 20.[54] Japan suspended its human papillomavirus vaccination program in 2013 (see "Barriers to vaccination" below) and restarted it in 2022. The suspension is estimated to have led to an additional 24 600 to 27 300 diagnoses of cervical cancer and 5000-5700 deaths from cervical cancer.[22 55]

Guidelines and recommendations

Several national and international vaccination schedules include human papillomavirus vaccination for primary prevention of cervical cancer, other human papillomavirus related cancers, and genital warts.[56-59] As of December 2021, all European Union/European Economic Area countries had human papillomavirus vaccination in their national vaccination schedules. Rwanda was the first African nation to implement a comprehensive human papillomavirus vaccination program in 2011 and is the only African country to meet the WHO target of a 90% vaccination rate for girls by age 15.[60] Whereas less than a decade was needed

Table 1 | Double blinded randomized controlled trials of human papillomavirus (HPV) vaccination (three doses) and efficacy

Study author, year; location	Trial description; type of vaccine; No of doses	No of participants; vaccination age	Follow-up (years)	Efficacy (95% CI)
Future II Study Group, 2007[36]; multinational	Quadrivalent *v* placebo; 3 doses	12 167; 15-26 years	3	98% (86% to 100%) CIN2+HPV 16/18 lesions
VIVIANE study (Wheeler et al, 2016)[37]; multinational	Bivalent *v* control; 3 doses	5747; >25 years	6.6	83.7% (47% to 100%) CIN2+HPV 16/18 lesions
PATRICIA trial (Paavonen et al, 2009)[38]; multinational	Bivalent *v* control; 3 doses	18 729; 15-25 years	2.9	92.9% (80% to 98%) CIN2+HPV 16/18 lesions
Huh et al, 2017[39]; multinational	Nonavalent *v* quadrivalent control group; 3 doses	14 215; 16-26 years	6	97.4% (85% to 100%) CIN2+HPV 31/33/45/52/58 lesions; 100% CIN2+HPV 6/11/16/18+lesions
Costa Rica Vaccine Trial (Porras et al, 2020)[40]; Costa Rica	Bivalent *v* placebo; 3 doses	7466; 18-25 years	11	97.4% (88% to 100%) CIN2+HPV 16/18 lesions

CI=confidence interval; CIN2+=cervical intraepithelial neoplasia 2 or 3 or adenocarcinoma in situ.

for 80% of high income countries to adopt human papillomavirus vaccination, only 41% of LMICs have been able to do so.[61]

All recommendations call for a two dose human papillomavirus vaccination schedule for girls aged 9-14 years, although the starting age varies across countries. If vaccination starts after age 15 or if the individual is immunocompromised, most recommendations are for three doses of vaccine.[56-58 62 63] These parameters are similar across countries with national programs, whether high income countries or LMICs. Catch-up vaccination of adults up through 26 years of age for those who have not previously been vaccinated or completed their vaccination series is recommended in most countries, but it is not included in all national programs.

The focus for most national programs is the younger adolescent group, although the nonavalent vaccine is licensed for use up to age 45 years in many countries. The US Centers for Disease Control and Prevention recommends shared decision making between patients and healthcare providers regarding vaccination for adults aged 27 through 45 years, as the public health benefit of human papillomavirus vaccination in this age range is minimal.[58] By contrast, the American Cancer Society does not recommend vaccination in the 27-45 age group, citing lower effectiveness and low potential for prevention of cancer for this group.[63] Ethical dilemmas exist regarding vaccination of older women and boys when access to vaccination is limited in the target adolescent female populations in LMICs, where the burden of cervical cancer is highest, vaccination rates are lowest, and reduction of cervical cancer is the main goal.

Assuming optimal supply and demand for human papillomavirus vaccination, the HPV-FASTER proposal describes an approach to offer catch-up vaccination to 26-45 year olds in combination with targeted cervical cancer screening to accelerate the near elimination of cervical cancer in central and eastern Europe, Latin America, Asia, and some parts of Africa.[64] The proposal indicates that systematic vaccination of women up to age 30, continued opportunity to vaccinate women up to 45-50 years, and an abridged number of visits for human papillomavirus based cervical cancer screening may be a cost effective strategy.[64] Cost effectiveness data from France indicate that 34% of ICC could be averted with vaccination up to age 40 years.[65]

A one dose human papillomavirus schedule can reduce infection and early stage disease according to nested observational and pilot studies (table 2).[66] In April 2022 WHO's Strategic Advisory Group

Table 2 | Population based observational studies of human papillomavirus vaccination (one, two, or three doses) and vaccine effectiveness

Study author, year; location	Trial description; type of vaccine; No of doses	No of participants; vaccination age	Follow-up (years)	Vaccine effectiveness (95% CI)
Pollock et al, 2014[41]; Scotland	National registries; bivalent; 3 doses	106 052; 20-21 years	<5	VE for CIN2 50%; RR 0.5 (0.4 to 0.63; P<0.001). VE for CIN3 55%; RR 0.45 (0.35 to 0.58; P<0.001)
Herweijer et al, 2016[42]; Sweden	National registries; quadrivalent; 3 doses	1 333 691; 13-30 years	<8	VE for CIN 2+, age <17 75%; IRR 0.25 (0.18 to 0.35). VE for age 17-19 46%; IRR 0.54 (0.46 to 0.64). VE for age 20-29: 22%; IRR 0.78 (0.65 to 0.93)
Kjaer et al, 2019[43]; multinational	National registry; 3 doses	2084; 15-26 years	12	CIN2+ VE 100%; IRR 0.0 (0.0 to 0.0)
Brotherton et al, 2019[44]; Australia	National registries; quadrivalent; 1, 2, and 3 doses	250 648; ≤15 years	<7	HR for CIN2+: 1 dose 0.65 (0.52 to 0.81); 2 doses 0.61 (0.52 to 0.72); 3 doses 0.59 (0.54 to 0.65)
Racey et al, 2019[45]; Canada	Provincial registries; quadrivalent; 1 and 3 doses	192 659; 9-14 years	7	VE for CIN2+: ≥1 dose 56.6% (42.1% to 67.7%); 3 doses: 57.9% (43.2% to 69.0%)
Rodriguez et al, 2020[46]; United States	US database; quadrivalent; 1, 2, and 3 doses	133 082; 9-26 years	5	HR for CIN2+: 1 dose 0.64 (0.47 to 0.88); 2 doses 0.72 (0.54 to 0.95); 3 doses 0.66 (0.55 to 0.80)
Shiko et al, 2020[47]; Japan	Japanese Cancer Society database; bivalent; ≥1 doses	34 281; 12-16 years	<5	CIN2+ VE 76%; RR 0.24 (0.10 to 0.60)
Verdoodt et al, 2020[48]; Denmark	National registries; quadrivalent; 1, 2, and 3 doses	590 083; ≤16 years	<9	VE for CIN2+ 57%

CI=confidence interval; CIN2+=cervical intraepithelial neoplasia 2 or 3 or adenocarcinoma in situ; RR=relative risk; IRR=incidence rate ratio; HR=hazard ratio; VE=vaccine effectiveness.

of Experts on Immunization updated its human papillomavirus vaccination dosing recommendations as follows: one or two doses for the primary target of girls aged 9-14 years; one or two doses for young women aged 15-20 years; two doses separated by six months for women older than 21 years.[67] A three dose schedule, if feasible, is still recommended for immunocompromised individuals, including women living with HIV.[67] If countries adopt this new single dose recommendation, barriers related to cost and access to vaccination could be overcome, especially in LMICs with low vaccination coverage.

Gender neutral vaccination programs

WHO's recommendation also allows for boys and men to get human papillomavirus vaccine on the same schedule as girls and women. Gender neutral human papillomavirus vaccination programs, which include both boys and girls, provide several benefits including more rapid population impact through herd immunity, indirect protection of unvaccinated women, and direct protection of boys and men, including men who have sex with men.[68] Although many high income countries have gender neutral human papillomavirus vaccination programs, around two thirds of the countries that provide human papillomavirus vaccine to adolescents do so only for girls.[69]

The human papillomavirus vaccination guidelines of the American Society of Clinical Oncology (ASCO), which stratify recommendations on the basis of resource settings, support extension of vaccination to boys in high resource settings if vaccine coverage is low (<50%) in the priority 9-14 year old female population. This is because the cost effectiveness of vaccinating boys for the purpose of cervical cancer prevention is low, unless vaccine coverage in the target population (girls aged 9-14 years) is also low.[57] Similarly, in resource limited settings, if human papillomavirus vaccination of girls is above 50%, ASCO recommends against vaccination of boys as this strategy is not thought to be cost effective for cervical cancer prevention, specifically. However, if resources allow, human papillomavirus vaccination can be extended to boys to prevent other human papillomavirus related cancers, and modeling shows that a gender neutral approach is cost effective when considering these cancers.[70]

Several studies have confirmed the cost effectiveness of a gender neutral strategy when considering the impact on all human papillomavirus related diseases, including penile and oropharyngeal cancer.[68 70] The US, Australia, and about half of European countries currently include boys in vaccination programs.[71] No country in Africa offers human papillomavirus vaccination to boys as part of its national program.[72]

Barriers to vaccination

Despite robust safety and clinical efficacy data, global human papillomavirus vaccination coverage for girls is approximately 18% for a first dose and 13% for series completion.[73] The WHO goal for human papillomavirus vaccination is 90% of girls fully vaccinated by their 15th birthday, but few countries have met or are anywhere close to this goal.[9] Whereas countries such as Australia and the UK have high human papillomavirus vaccination coverage, the US is far from its goal of 80% coverage for boys and girl aged 13-15 years.[74] Human papillomavirus vaccination is marked by disparities, with much lower uptake in LMICs where the burden of ICC is highest; few of these countries even offer human papillomavirus vaccine as part of their national immunization schedules.[9] Figure 2 illustrates global differences in human papillomavirus associated cancers.

Global human papillomavirus vaccination coverage dropped for the first time in 2020.[46] Most affected were the Americas and Africa; by contrast, other areas had small increases. Owing to a drop in well child visits, which persists to date, the US provided several million fewer doses of human papillomavirus vaccine in 2020-22 than would be expected on the basis of 2019 levels.[75] Several factors related to supply and demand account for low uptake of human papillomavirus vaccination, even before the pandemic. On the supply side, the cost of human papillomavirus vaccines makes them unaffordable for many LMICs and disproportionately accessible to high income countries. A previous worldwide shortage of the vaccines limiting availability for LMICs has abated, and efforts by Gavi, the Vaccine Alliance, WHO, and other organizations to provide the vaccines at dramatically lower costs have increased access in LMICs. Finally, a continued logistic barrier to administration of vaccine is that currently licensed human papillomavirus vaccines all require refrigeration.

On the demand side, misinformation, cultural views on sex, and mistrust of the medical system have contributed to low confidence in the vaccine by parents. Programmatic problems have further limited demand in some areas. Some countries have experienced unsubstantiated safety scares around the vaccine, which led to drops in coverage. In 2013 the national immunization program in Japan was suspended owing to reports of adverse events in girls, leading to vaccination rates going from 70% to less than 1% of eligible girls.[76 77] After further safety data, reassurance from WHO, insistence from Japanese academic societies, and Japanese data indicating that similar symptoms occurred in unvaccinated girls, the program was restarted in 2022.[76] The importance of the voices of political and public health leaders was also shown when a national information campaign helped Denmark's human papillomavirus vaccination rates to rebound four years after negative media coverage started in 2013.[78] Pan American Health Organization countries are using monitoring of social media and proactive social media campaigns to manage negative information and rumors that have been associated with low vaccination uptake in the region.[61 79]

In settings where limited supply is not a problem, demand plays a role in how individuals access a vaccine. Delegation of promotion of vaccine to individual providers or even the manufacturers has been less effective than centralized and integrated efforts. In particular, promotion by industry seems to have unsettled some parents.[80] School located provision reliably yields the highest coverage,[81] but many countries continue to rely on provision in primary care settings or pharmacies.

Opportunities to reduce the barriers discussed above include securing sufficient and affordable vaccine doses, school located delivery of vaccination, registries, innovations in communication to combat misinformation about vaccines, and implementation of supportive national recommendations and policies.[9] Community based strategies should also be present for girls who do not attend school. New recommendations for one dose vaccination schedules in adolescent girls will help to mitigate problems with high cost and potential shortages if adopted widely and may increase demand if only a single dose is needed. Changes in the formulation of vaccines to limit need for refrigeration and co-formulation with other vaccines will also increase access.[12]

Owing to controversies about human papillomavirus vaccination, proactive television, radio, or social media communication strategies to quickly combat rumors and misconceptions are needed.[61 79] Improving provider recommendations will build confidence about and demand for the vaccine. Increasing public understanding of the impact of human papillomavirus vaccination on the risk of cervical cancer and other anogenital and head and neck cancers may provide an additional impetus for vaccination.[82] Traditional venues for awareness campaigns must be adjusted by understanding how women and parents obtain information online and working within these platforms. Strategies that benefit LMICs may also work in high income countries to reach historically marginalized girls and women with less access to vaccination and screening and higher risk of cervical cancer.

Combined human papillomavirus vaccination and cervical cancer screening

WHO and US, European, and Australian organizations have called for the near elimination of cervical cancer. A statistical modeling study based on high quality cancer registry data of worldwide trends in ICC developed from the International Agency for Research on Cancer's Cancer Incidence in Five Continents series shows a way forward. According to data from 37 registries in 20 countries, with no changes in rates of human papillomavirus vaccination or cervical cancer screening, the annual number of ICC cases globally will increase from an estimated 600 000 in 2020 to 1.3 million in 2069 as a result of increases in population, aging, and underlying risk factors for exposure to hrHPV.[83] An estimated 44.4 million women will be diagnosed as having ICC during this time period, with two thirds of these cases being in LMICs. However, assuming a rapid scale up of human papillomavirus vaccine coverage to more than 80% of adolescent girls along with continued or increased screening for cervical cancer in adult women, an estimated 13 million cases of ICC could be averted in LMICs. This type of global strategy could lead to an incidence of ICC of less than four per 100 000 women across all countries worldwide—similar to the proposed WHO goal for the near elimination of cervical cancer.[9 83] Secondary prevention through screening for cervical cancer remains essential to prevention of ICC, especially in older women and women living with HIV because these women either are not eligible for vaccination or have a higher risk of cervical pre-cancer and cancer.

WHO's near elimination plan's foundation is based on attainment of several of the sustainable development goals such as ending poverty, ensuring access to sexual and reproductive healthcare, gender empowerment, and reduction of inequality among countries.[9] Interventions specific to cervical cancer include primary prevention through human papillomavirus vaccination in 9-14 year olds and secondary prevention in women over 30 years old through screening and treatment of cervical pre-cancer.

The need for innovation in cervical cancer screening will remain relevant even in countries that reach high vaccination rates, as high vaccination coverage may eventually reduce the accuracy of current cervical cancer screening methods. As cervical cancer becomes rarer, the ability of our screening tests to detect cases will drop and the rate of false positive screening results and associated over-testing, over-treatment, and avoidable harms will increase. Although data on the beneficial effect of widespread human papillomavirus vaccination are compelling, no country is at the stage to consider reducing screening for cervical cancer as a result of human papillomavirus vaccination, particularly with lapses in preventive healthcare with the covid-19 pandemic.

Emerging vaccine options

In 2022 the Serum Institute of India announced the development of a quadrivalent prophylactic human papillomavirus vaccine (estimated cost of $2.50 to $5.00 per dose) which will become available in India in 2023 and for export in 2024.[84 85] Given that cost has been a major barrier to expansion of human papillomavirus vaccination coverage, the availability and efficacy of this new vaccine will be a major game changer in efforts to prevent cervical cancer. A phase 3 clinical trial for an 11 valent prophylactic vaccine is ongoing in China (ClinicalTrials.gov NCT05262010). Several trials of next generation vaccines are planned or ongoing using L2 rather than the currently licensed vaccines with L1 virus-like particles to develop an antigen response, meaning that the vaccine will probably not require refrigeration and allowing cross protection over multiple genotypes.

Additional clinical trials of currently licensed human papillomavirus vaccines are being conducted with focus on populations at risk such as transplant recipients (NCT03036930) and people with HIV (NCT04982614, NCT05495906), as well as dose reduction studies in adolescents, people with HIV, and boys and men (NCT03728881, NCT04688476, NCT03943875, NCT03832049, NCT05495906, NCT05173324, NCT04953130). Further research into use of the nonovalent vaccine as an adjuvant to excision for cervical pre-cancer is ongoing (NCT03848039).

Therapeutic vaccines studies using cell mediated immunity against existing infection have shown little success to date.[86] Current trials are studying novel vaccines for adjuvant treatment of cervical cancer and other diseases caused by human papillomavirus (NCT04800978, NCT04084951, NCT02405221, NCT04432597, NCT00788164, NCT0341848, NCT03947775).

Conclusion

Human papillomavirus vaccination is highly effective in preventing infection with the virus,[87] cervical pre-cancers,[52] ICC,[53] and several other diseases.[88] The near elimination of cervical cancer is possible in countries with robust uptake of the vaccine. Opportunities to increase the uptake of human papillomavirus vaccine exist in several domains. However, vaccine distribution continues to be inequitable among and within countries according to income, race/ethnicity, and gender. Given global disparities, most LMICs will be delayed by decades in achieving, or will never achieve, near elimination of cervical cancer. The covid-19 pandemic has further set some countries back. Deliberate action will be needed to unwind these deeply rooted inequities. Inaction will only perpetuate them, further widening the gap between countries and people of wealth and those who are less privileged.

ICC is a preventable cancer affecting millions of women worldwide. Near elimination of ICC will require new partnerships between leaders in public health, governments, non-governmental organizations, communities, and patient advocates along with the healthcare teams who see patients. Advancement of the single dose strategy, development of low cost vaccines, co-formulation of human papillomavirus vaccine with other routine vaccines that do not need refrigeration, and combating vaccine misinformation are areas of necessary research and policy change.[12] Action in these areas and other initiatives to increase the supply of and demand for human papillomavirus vaccination, particularly in marginalized or remote populations and LMICs, are essential.

QUESTIONS FOR FUTURE RESEARCH

- How can a human papillomavirus vaccine be developed that does not need to be refrigerated, to support low and middle income country settings where refrigeration is not reliably available?
- How can health workers in low and middle income countries most effectively recommend human papillomavirus vaccination?
- What level of human papillomavirus vaccination coverage could affect cervical cancer screening guidelines?
- How will herd immunity for human papillomavirus affect the risk for or incidence of other human papillomavirus related cancers or non-cancer related outcomes?

PATIENT INVOLVEMENT

A draft of the article was reviewed by a group of cervical cancer survivors and members of the non-profit cervical cancer and awareness group, Cervivor, located in the United States. After giving informed consent, another cervical cancer survivor affiliated with the cancer support network SHARE gave the following perspective: "After many trips to my local health department and misdiagnosis of symptoms which I was told were related to a bacterial infection, I was diagnosed with cervical cancer, which later metastasized. Had the human papillomavirus vaccine been available when I was a teenager, my life would have taken a very different direction. I was not only infected with human papillomavirus once, but with two different types, one of which ultimately led to cancer. I feel as though my socioeconomic situation played a huge role in my largely flying under the radar. Having the option to vaccinate can help people around the world who struggle with access to care not have to navigate treatment of a cancer diagnosis."

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Contributors: LR had the idea for the article, did the literature search, and led the writing of the manuscript. CM, SO, CJC, and NTB contributed to the writing of the manuscript. LR is the guarantor.

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