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SPECIAL REPORT

Scientific approaches toward improving cervical cancer elimination strategies

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Abstract

At the 2023 EUROGIN workshop scientific basis for strategies to accelerate the elimination of cervical cancer and its causative agent, human papillomavirus (HPV) were reviewed. Although some countries have reached key performance indicators toward elimination (>90% of girls HPV vaccinated and >70% of women HPV screened), most are yet to reach these targets, implying a need for improved strategies. Gender-neutral vaccination, even with moderate vaccination coverage was highlighted as a strategy to achieve elimination more rapidly. It is more resilient against major disturbances in vaccination delivery, such as what happened during the coronavirus pandemic. Further, an analysis of ethical/legal issues indicated that female-restricted vaccination is problematic. Extended catch-up of vaccination with concomitant screening, and outreach to vulnerable groups were highlighted. Although birth cohorts with high coverage of HPV vaccination at school are protected against HPV, and HPVs have a very low reproductive rate in women above age 35, adult women below age 30 have inadequate direct protection. In addition to herd protection from gender-neutral vaccination, this group can be protected by offering concomitant catch-up HPV vaccination and HPV screening. Furthermore, hepatitis B vaccination experiences indicate that elimination cannot be achieved without prioritizing vulnerable/migrant populations. The long-lasting durability of vaccination-induced antibody responses suggests prolonged protection with HPV vaccines when adequately administrated. Finally, cost-effectiveness modelling suggests that high-coverage HPV vaccination in multiple population segments will be resource-saving due to reduced need for screening. In summary, the workshop found that strategically optimal deployment of vaccination will accelerate elimination of HPV and cervical cancer.

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KEYWORDS
gender-neutral, HPV, population immunity, screening, vaccination

What's new?

Although some countries have reached key performance indicators toward the elimination of cervical cancer and its causative agent, human papillomavirus, most are yet to reach the vaccination and screening targets. The scientific basis for strategies to accelerate the elimination of cervical cancer was recently reviewed at a dedicated 2023 EUropean Research Organization on Genital Infection and Neoplasia (EUROGIN) workshop. The reviewed evidence suggests that strategies with more ambitious use of human papillomavirus vaccines (gender-neutral vaccination or concomitant vaccination and screening) would accelerate elimination of human papillomavirus and cervical cancer.

1 | INTRODUCTION

Both HPV infections and cervical cancer are still common despite it being 40 years after discovery of human papillomavirus (HPV) type 16, the major cause of cervical cancer, 15 years after licensure of efficacious prophylactic HPV vaccines (https://www.ema.europa.eu/en/medicines/human/EPAR/cervarix/gardasil/gardasil9, Accessed March 2023), and after demonstration of the effectiveness of HPV-based cervical screening.[1] What can be done to improve the impact of HPV vaccination and HPV screening to accelerate the elimination of cervical cancer? This goal is defined by the World Health Organization as a reduction in cervical cancer incidence to levels below 4 new cases per 100,000 women per year.[2,3] The scientific basis and strategies for attaining this worthwhile goal were the topic of a workshop at the 2023 EUROGIN conference in Bilbao, Spain.

Up-to-date knowledge on the worldwide coverage of HPV vaccination and primary HPV screening, the two interventions for the elimination of cervical cancer,[4,5] is the starting point on which all attempts to improve the preventive efforts must be based. Due to the low basic reproduction number (R_0) of most HPV types moderate coverage girls-only HPV vaccination already has had an impact on the prevalence of many genital HPV types at the population level. HPV16 which is responsible for half of cervical cancers has a higher reproduction rate than other HPV types, and as such >90% girls-only HPV vaccination coverage is required to achieve elimination.

Gender-neutral vaccination has been evaluated in a randomized trial, which found that elimination can be achieved with moderate coverage scenarios applying only this strategy.[6,7] Moreover gender-neutral vaccination accelerates elimination as herd effect is rapidly established when both genders are protected instead of just one.[6,7] Aside these empirically verified differences, a thematic analysis suggests that gender-restricted vaccination policies have ethical and legal pitfalls not coherent with public health goals.[8]

We have a good understanding of the mode of action of vaccine-induced protection. The available vaccines induce sustainable total and high neutralizing antibody levels, which can be measured and used as outcomes in HPV vaccine research, for example, when evaluating new vaccine candidates and/or modes of administration.[9,10] The long durability of antibody responses is essential for designing resilient programs. The coronavirus pandemic showed how unforeseen events can disrupt vaccination and screening programs. Designing programs that can withstand disturbances in the delivery of interventions is of paramount importance in disease prevention.[11,12]

In most countries adult women younger than 30 years are at risk of HPV infection but not fully vaccinated against HPV. This implies a need to offer protection to this age group. As many young adult women may already have been exposed to HPV extended catch-up vaccination needs to be combined with HPV screening to provide them full protection. A country-wide trial of this strategy targeting women aged 23–29 is underway in Sweden.[13] Vulnerable female groups missed by health services due to neglect or because they are out of healthcare reach represent an additional population segment that must be targeted by both indirect (herd effect) and direct elimination efforts.[14] Finally, cost-effective analyses suggest that ambitious HPV vaccination strategies may result in both HPV elimination and cost-savings[15] because of a reduced need for subsequent screening. All above issues and objectives are elaborated in more detail in the following sections.

2 | WORLDWIDE HPV VACCINATION AND SCREENING COVERAGE

In 2020, the WHO approved the plan toward the elimination of cervical cancer as a public health problem. The WHO cervical cancer elimination strategy includes coverage targets for scale-up by 2030 of HPV vaccination to 90% of all adolescent girls, twice-lifetime cervical screening to 70%, and treatment of pre-invasive lesions and invasive cancer to 90%.[16] Based on the results from WHO/UNICEF estimates of national HPV immunization coverage[17] and the new global estimates on cervical cancer screening[5] we are still far behind of reaching these goals. In females global HPV vaccination coverage for 2021 is estimated to be 12%, while lifetime screening coverage in women aged 30–49 years by 2020 is reported to be 36%[5,17,18] (Figure 1). However, significant disparities across different populations and regions are masked behind these figures.

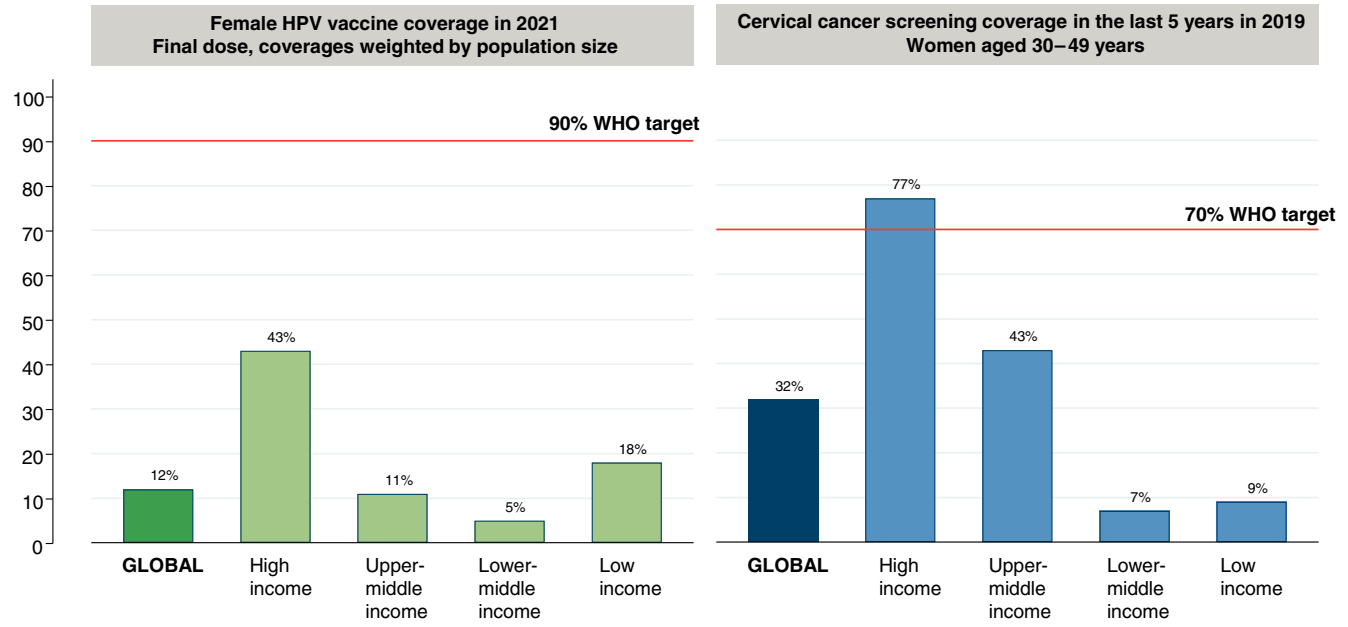

FIGURE 1 Global estimates of HPV vaccine coverage and cervical cancer screening by income. HPV screening >50% of all cervical screening in high income countries only.

By the year 2023, HPV vaccination programs have been introduced in 126 (66%) of the 194 WHO Member States. The Americas, Europe, and Oceania are the regions with the highest introductions, with 89%, 84%, and 81% of their countries having introduced the HPV vaccine respectively, while Asia and Africa are at ~50%. Despite a high number of introductions, 59% of girls still live in countries that have not yet introduced, significantly impacting global coverage levels. However, many countries that do not currently vaccinate are planning to introduce the vaccine, with 20 countries, representing 26% of global cervical cancer burden, announcing plans to do so within the next 2–3 years. In 2022, 11 new countries introduced HPV vaccination programs.

According to data from the WHO/UNICEF annual Estimates of National HPV Immunization Coverage, program performance in many countries, including high-income countries, remains sub-optimal.[2,4] In 2019, before the pandemic, programs had an average coverage of 67% for the 1st dose of the vaccine and 53% for a 2nd dose. However, these averages dropped by 10 percentage points after the pandemic, especially in low- and middle-income countries (LMICs). LMICs had better coverage for the 1st dose, but lower for the 2nd dose due to higher dropout rates. In 2019, only 5(6%) countries achieved coverages with the 2nd dose of more than 90%, 22 countries (21%) achieved coverages of 75% or higher, whereas 35 (40%) had a 2nd dose coverage of 50% or less.[4]

When expressed as world population coverage (ie, weighted by population size), global HPV vaccine coverage (2 doses) for 2021 is estimated at 12%, compared to 15% in 2019. This global estimate had been on an increasing trend for several years, largely due to the number of new introductions. However, the trend has reversed in the last 2 years due to the pandemic. There remains a long way to go to meet the 2030 elimination target of 90% of girls vaccinated. Not only is there a need to expedite introductions, but also it is critical to improve program performance and deploy catch-up vaccination to girls in the recommended vaccination ages.

In combination, vaccination and screening accelerate progress toward cervical cancer elimination. For example, a twice-lifetime HPV screening is estimated to avert 12 M cervical cancer cases within a century in comparison to the 61 M cases predicted to be averted by HPV vaccination.[19] Elsewhere, we describe the status of cervical screening programs worldwide, including the adoption of HPV-based strategies, and the methods and results for the first edition of WHO coverage estimates of cervical cancer screening.[5] The extent/organization of cervical screening varies greatly across the globe.[18,20] Of 202 countries evaluated, only 139 (68%) had identifiable recommendations for screening.

Among these, only 48 countries (predominantly high-income and upper-middle-income) had implemented or were implementing HPV-based primary screening. Globally, 64% of women aged 30–49 years have never been screened for cervical cancer, representing 662 million women in the target age group of the WHO elimination strategy. Estimated worldwide coverage in women aged 30–49 years in 2019 was 15% in the previous year, 28% in the previous 3 and 32% in the previous 5 years, and 36% ever in the life-time. There are significant global disparities in cervical cancer burden and prevention. In high-income countries, 84% of women aged 30–49 years had at least one screening in their lifetime, compared to 48% in upper middle-income countries, 9% in lower-middle-income countries, and 11% in low-income countries. Roll-out of HPV screening is very low in low-income and middle-income countries, where the burden of disease is highest. The priority of the WHO elimination campaign should be to increase both HPV screening coverage and treatment of detected lesions. Challenges of surveillance systems in both coverage and quality control remain.

TABLE 1 The number of vaccinated female birth cohorts needed for effective elimination (95% reduction in the subsequent birth cohorts) of the life-time incidence of oncogenic human papillomaviruses (HPV) by HPV type, vaccine efficacy (VE) and coverage compared to the pre-vaccination era (naïve birth cohorts).

		Coverage of vaccination			
	VE	95%	90%	75%	50%
HPV16	95%	24	NA	NA	NA
HPV18	95%	6	9	NA	NA
HPV31/33/45/52/58	95%	3	5	11	NA
	80%	9	10	31	NA
	50%	NA	NA	NA	NA
HPV35/39/51	95%	1	3	7	12
	80%	6	6	9	16
	50%	12	13	18	NA

3 | ELIMINATION OF CERVICAL CANCER BY STRATEGICALLY COMBINING HPV VACCINATION AND HPV SCREENING: THE "EVEN-FASTER" MODEL

3.1 | Concept

Organized, school-based HPV vaccination will result in population immunity when the children become adults. After incident HPV infections have been eliminated an organized, population-based HPV-based cervical screening effort will eliminate cervical cancer when the entire population has been screened for HPV. We wished to investigate if the timepoint for elimination of HPV infection could be accelerated by targeting ample numbers (Table 1) of birth cohorts at risk of HPV transmission and sub-optimal immunity with an extended and fast catch-up of HPV vaccination.

In Sweden, there is very little HPV among women younger than 23 as these women have been vaccinated by a high coverage school-based HPV vaccination program. It is primarily women (and men) ages 23–30 that are still propagating HPV (as evidenced by an age-specific effective reproduction number R >1.0).[21] In 2021, we therefore launched a nationwide population-based study offering all females in the country who are aged 23–28 concomitant HPV-vaccination and HPV-screening (NCT04910802). We revised the concept of concomitant HPV-vaccination and HPV-screening of fertile-aged women[22] by concentrating on those birth cohorts that are still sustaining the HPV infection—thereby achieving an even faster elimination of cervical cancer.

3.2 | Context

Girls ages 10–12 have been systematically offered HPV vaccination in schools since 2012 (birth cohorts born 1999 and later). When the HPV vaccination program started, girls ages 13–18 (born 1993–1998) were also offered catch-up vaccination. However, coverage achieved by this effort was on average 55%–60%, probably enough for fast clearance high-risk HPV types (Table 1) but not high enough to reach HPV16 elimination.[3,6]

HPV vaccination is effective also in older women, provided that they are HPV-negative at vaccination (per protocol population of women naïve at vaccination). A registry-based cohort analysis of the effect of HPV-vaccination in Sweden showed that among women vaccinated before age 17, the decrease in cervical cancer was 88% as compared to unvaccinated women between the ages of 17–30 where it was only 53%.[23] These women were not HPV tested at vaccination and therefore correspond to the Intention-to-treat population in vaccination trials. Therefore, to achieve maximal protection of the young adult women, they should be offered concomitant HPV screening and HPV vaccination. Among women under 30, screening coverage has been over 85% for the last 10 years (www.nkcx.se), and the cervical screening program thus provides a framework to reach a high proportion of the population of young women also with HPV-vaccination. HPV-positive women will be followed up in the established algorithms of the screening program.

3.3 | Implementation

Organized cervical screening is offered with sampling by midwives at maternity care centers or by HPV self-sampling. HPV vaccination status is checked and vaccines are given by the midwives at the routine cervical screening visit or at a vaccination center that distributes self-sampling kits. We have trained >1000 midwives across the country in vaccinology. The study was piloted in one region in 2021 and currently all 21 regions in the country participate. Women provide informed consent and enter a health declaration in an online Clinical Trials System. All results (both from the study and from all other healthcare facilities in Sweden) of cervical samples (HPV tests, histopathological diagnoses) are collected to the National Cervical Screening Registry (www.nkcx.se). The main outcome is whether or not the HPV infection is eliminated from the young adult Swedish females at a follow-up visit 3 years later.

3.4 | Generalization and considerations

The selection of target birth cohorts for the Swedish "even faster" study has been made based on age-specific effective R value estimations of HPV infection in Sweden. Here R is dependent on HPV type[4] and contact mixing pattern in the population.[3] Using the R to design focused campaigns for accelerated HPV elimination can be applied to any population where it can be calculated. With the WHO recommended girls-only vaccination the ample number of birth cohorts needed to be vaccinated (Table 1), time between achieving sufficient population immunity and achieving HPV elimination is impacted by type-specific duration of HPV infections.[24] If the infection is not transmitted before clearance, fade-out will come as quickly as

population immunity is achieved. Furthermore, the timeframe to elimination is impacted by how long it takes for a persistent HPV infection to develop into a precursor lesion that can be treated.

The Swedish "even faster" study is supported both by research funding as well as a specific line item in the national budget, decided upon by parliament. This one-time effort and represents a concentrated effort to harness the impact of highly effective HPV vaccines and HPV-screening.

4 | GENDER-NEUTRAL VACCINATION TO PROTECT ALSO UNVACCINATED MARGINALIZED WOMEN

If 90% of all girls around the world are vaccinated against HPV by the age of 15 by the year 2030,[25] the remaining 10% of girls can be protected from HPV infection and associated cancers by herd effect, which refers to the indirect protection of the unvaccinated in a population due the many immune individuals reducing transmission within that population.[26] The degree of vaccine-induced herd protection is dependent on vaccination coverage, the population, and the distribution of HPV types.[27,28] For each HPV type there is a critical vaccination coverage threshold at which the HPV type may be eliminated.[26] If the vaccination coverage within a defined geographic population is greater than this threshold, then the herd immunity will result in the elimination of HPV infection in that population.[3,21,29] This coverage threshold is dependent on the HPV vaccine efficacy and the R_0, of the HPV type, which is both HPV type specific and population-specific.[6] The R_0 and resulting critical vaccination coverage is higher for HPV16, the most oncogenic HPV type, than for other high-risk HPV types. In the setting of Finland, the R_0 for HPV16 was estimated as 3.3 compared to 2.2 for HPV18, resulting in a critical HPV vaccination coverage of 95% for HPV16 and 82% for HPV18 if only girls are included in the Finnish vaccination program.[6]

It is crucial that the delivery of the cervical cancer prevention strategy be equitable. Among women in Sweden from the birth cohorts who were eligible for opportunistic vaccination, the unvaccinated women were less likely to attend the cervical cancer screening program than the HPV vaccinated women.[23] Marginalized women have a long trajectory of missing multiple preventive opportunities.[14] However, when organized free-of-charge HPV vaccination was introduced in schools, the differences in socio-economic factors between the vaccinated and unvaccinated were greatly reduced and vaccine uptake greatly increased.[14]

In national vaccination programs targeting only girls, HPV vaccination coverage is very rarely above 95%.[8] Therefore, realistic and achievable HPV vaccination strategies to enhance the herd protection against HPV16 infection are necessary. In 2007, a large population-based community randomized trial was initiated in Finland to compare the effectiveness of school-based gender-neutral HPV vaccination to girls only-vaccination.[30] Thirty-three geographically distinct communities/cities were randomized to implement either gender-neutral HPV vaccination, girls-only HPV vaccination or gender-neutral vaccination with a control vaccine.[30] During 2007–2010, the 1992–1995 birth cohorts in these communities were invited to receive HPV vaccination according to communities' allocated strategy, when the early adolescents were 12–15 years old.[30] The vaccine up-take was moderate, with ~45% coverage among the females from the two intervention arms and 20% among the males (in the gender-neutral intervention arm).[6] When the women from the birth cohorts were 18 years old, the HPV prevalence was estimated among the unvaccinated women. A distinct 59% reduction in vaccine-targeted and cross-protected HPV18/31/33 was observed after gender-neutral vaccination,[6] but no reduction in the HPV16 prevalence.[6] Nevertheless, when measuring the cumulative incidence of HPV16 infection (via seroprevalence), a marked reduction also in HPV16 cumulative incidence was observed among the unvaccinated women in the post-trial era as compared to the pre-trial era.[7] This reduction in cumulative HPV16 incidence among the unvaccinated was only found in the communities where there had been gender-neutral vaccination.[7]

Previously it had been suggested that it may be harder to establish herd protection among the highest sexual risk-taking group than among the rest of the population. The reduction in cumulative HPV16 incidence was observed also among the unvaccinated women with the highest sexual risk-taking behavior in the communities where there had been gender-neutral vaccination.[7]

If HPV vaccination coverage and the vaccination strategy are not optimal the intervention may only result in a partial herd effect which will still result in some unvaccinated women contracting HPV16 infection. However, if the vaccination strategy is gender-neutral and the vaccination threshold is ramped up to the country-specific critical vaccination threshold for HPV16 then it will be possible to eliminate HPV16 and HPV18 from that country.[3,6,7] For Finland, the critical vaccination coverage for HPV16 has been estimated to be 74% with gender-neutral HPV vaccination. Results from a modeling study have indicated that in the Finnish setting if gender-neutral vaccination with 75% vaccination coverage is applied, then the incidence of HPV16 can be reduced to zero in all age groups 30 years after vaccination is implemented.[3] The elimination of HPV16 from a population will be the soundest way to protect the HPV unvaccinated women in that population.

Therefore, to protect marginalized unvaccinated women from the risk of HPV16/18 associated cervical cancer, HPV vaccination should be implemented based on the following requirements: (a) gender-neutral, (b) delivered in an equitable manner, for example, in a country with high rates of school attendance, this may be achieved via free-of-charge school-based vaccination and (c) at a vaccination coverage equal or higher than the country-specific critical immunization threshold. It is also important to implement a comprehensive and tailored cervical cancer prevention strategy for all immigrants and migrants with concomitant HPV vaccination and HPV screening.

5 | ETHICAL AND LEGAL ISSUES RELATED TO HPV VACCINATION POLICY

As previously discussed, to achieve HPV and cervical cancer elimination a primary goal is to have 90% of females vaccinated against

HPV.[31] This goal does not include vaccinating males who are also impacted by HPV-associated disease burdens. In 2019, HPV vaccine supply constraints led the Strategic Advisory Group of Experts on Immunization to prioritize female HPV vaccination.[32] HPV vaccine supply has rapidly increased but in 2020 the WHO estimated that HPV vaccine supply would not meet demand.[33]

On the surface, the WHO's gender restriction seems to systematically deny an equal right for marginalized populations to acquire protection from HPV-associated cancers. However, with the insufficient vaccine supply at that time, we contextualized the strategy within health equity and policy. We conducted a narrative review and identified legal and ethical issues pertaining to the gender restriction of HPV vaccination.[8] In our study, we identified six ethical constructs and one legal construct which highlight important considerations for marginalized individuals, specifically males, not receiving direct interventions (Figure 2). Excluding males from HPV vaccination negatively impacts all individuals regardless of sex. HPV prevention is left to females, and without targeted intervention, males are less aware of both HPV and HPV-associated diseases. Men who have sex with men as well as unvaccinated females remain unprotected despite herd immunity and cross protection. Questions are raised as to whether resources should be allocated toward male vaccination or increasing vaccination coverage in females. Females receive additional protection through the well-developed screening techniques for cervical cancer, whereas males receive minimal to no benefit from secondary prevention as screening for HPV-associated cancers other than cervical cancer is not common medical practice. From a standpoint of equity and social justice, everyone, regardless of sex should have access to timely HPV vaccination. Vaccine mandates could help to increase vaccination rates and overall population-level protection against HPV. Without gender-neutral vaccination, however, a vaccination law may be discriminatory based on sex. Although the benefits of gender-neutral vaccination seem to outweigh the drawbacks, looking beyond the vaccine shortage, there are economic arguments that do support the female-only HPV vaccination strategy. Males have a lower disease burden of HPV-associated cancers[34] and with high female vaccination coverage, gender-neutral vaccination is less cost-effective because males receive some protection.[35,36] Our identified legal and ethical constructs are important considerations for implementing or withholding gender-neutral vaccination, and they can be generalized to multiple scenarios in which individuals or at-risk groups need to be prioritized for HPV vaccination.

Although the supply problem was less severe in 2022 than during the immediate pre-pandemic period, our findings are still pertinent for HPV vaccine policy. The global HPV vaccine shortage has been partially ameliorated and, recently, the WHO projected that supply was expected to meet demand for a two-dose schedule for females, including planned multi-age cohort catch-up vaccination, but with no new gender-neutral programs.[37] Further efforts are needed to sustainably increase resources. Historically, HPV vaccination evolved from a recommended three- to two-dose schedule starting from North America.[8] Recently, SAGE concluded that one dose provides adequate protection against cervical cancer and recommended updating dose schedules,[38] which could aid in expanding vaccine availability. Clinical development of existing and novel vaccines could further increase vaccine availability. Two novel vaccines, Cecolin (bivalent), and Cervavac (quadrivalent) have recently passed phase 3 clinical trials. Cecolin received licensure in 2019[8] and Cervavac was launched in January 2023.[39] In addition to improving vaccine availability, there are other barriers to HPV vaccination that must be addressed. Vaccine

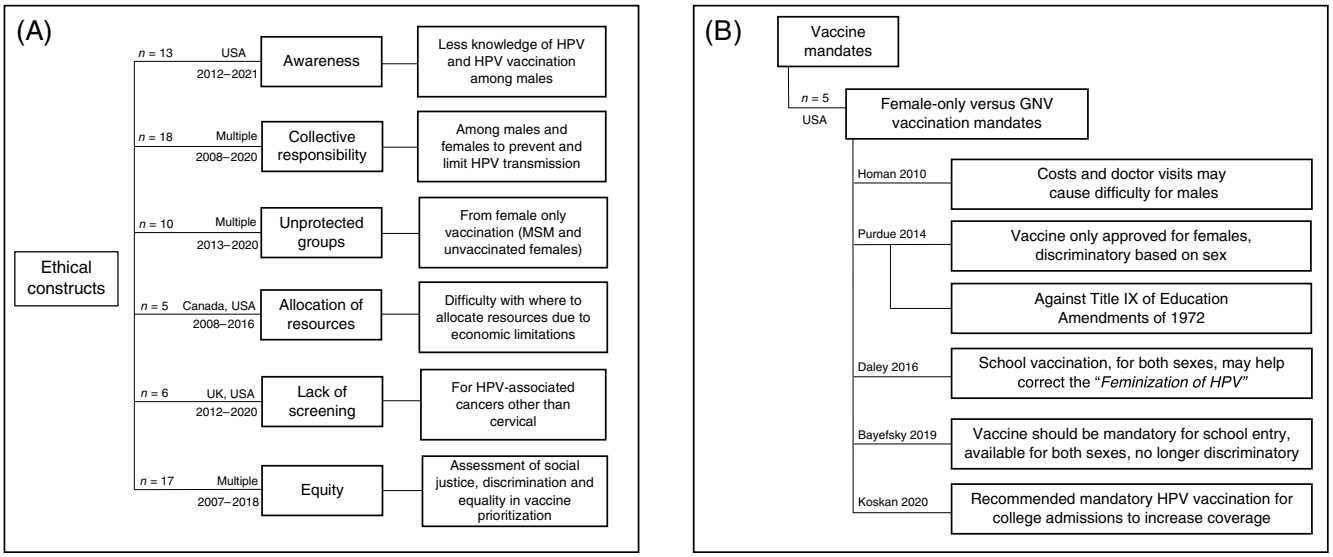

FIGURE 2 Summary of the ethical (Panel A) and legal (Panel B) constructs of GNV identified by Logel et al.[8] Six ethical constructs were identified through thematic analysis (Panel A): awareness, collective responsibility, unprotected groups, allocation of resources, lack of screening and equity. Panel A shows the number of articles discussing the ethical construct (*n*), the publication range, country of the majority of records and main findings. One legal construct was identified relating to vaccine mandates (Panel B). Panel B shows the number of articles discussing the legal construct (*n*), country of all records, and the specific findings from each identified article overtime.

affordability continues to hinder several countries' planned introduction of HPV vaccination programs.[37] There are further obstacles to HPV vaccination to be considered, such as vaccine hesitancy and acceptance. Our study's findings[8] can assist the debate on how to address these issues.

Ultimately, there is an ethical dilemma in vaccine prioritization. This dilemma is further exacerbated by insufficient HPV vaccine availability. However, principles of health equity and policy should take precedence over logistical issues. The ethical and legal constructs we established as foundational to assessing vaccine prioritization reach beyond scientific and economic evidence to determine how to most justly protect resource-denied groups against HPV-associated diseases.

6 | SUSTAINABILITY OF HPV VACCINE-INDUCED PROTECTIVE ANTIBODIES

While initial HPV vaccine trials used both antibody levels and observed efficacy against persistent infection and pre-malignant cervical lesions, there is today consensus that HPV vaccination trials can use immunobridging data and non-inferiority criteria of antibody levels. This is clearly pertinent, given the accumulated data on HPV vaccination trials over the last 15 years, and follows on the evidence that the mechanism of vaccine-induced protection relies on the induction of strong anti-HPV antibody responses. Caveats, however, are the lack of formally defined minimal protective anti-HPV antibody levels and the absence of robust evidence from trials in global regions bearing the highest burden of HPV-related morbidity and mortality.

In the early HPV vaccine trials, antibody-induced neutralization responses measured in vitro are well correlated with the estimated study endpoints, that is, vaccine efficacy against virus-related persistent infection[40,41] and pre-malignant cervical lesions.[42,43] Recent studies with 3-dose (multidose) cohorts have reported sustainable binding and neutralizing antibody levels to vaccine HPV types 16/18 for longer than a decade in recipients of the bivalent and quadrivalent vaccines (Figure 3).[10,44,45] HPV18 neutralizing antibody levels waned considerably in a minor but relevant portion of the quadrivalent vaccine recipients. Fourteen percent of the quadrivalent vaccine recipients followed up by a population-based cohort in Finland had neither detectable total nor neutralizing antibody levels 2–4 years after vaccination, whereas all bivalent vaccine recipients were HPV18 neutralizing antibody seropositive for up to 12 years post vaccination.[10,44] Consistent with the above findings, the 10-year immunogenicity follow up with participants of the IARC trial in India reported a similar lack of HPV18 neutralizing antibodies in 16% and 18% of quadrivalent vaccine recipients 10 years post-administration of, respectively, 3 and 2 vaccine doses. In the same IARC trial, more than half (51%) of quadrivalent vaccine recipients were HPV18 neutralizing antibody negative at year 10 when 1-dose vaccination was administered.[46] In this context, recent DoRIS study data is noteworthy.[47] In spite of robust antibody responses to HPV16 and HPV18 up to 2-years post vaccination following a single dose of either the bivalent or nonavalent HPV vaccines in adolescent girls aged 9–14 years, the HPV18 seropositivity at month 24 did not meet non-inferiority criteria for single dose compared to multidose schedules for either vaccine.

An important aspect to be addressed on the pursuing of the WHO call for cervical cancer elimination[48] should be a continued vaccine-induced protection against HPV types other than 16 and 18. In this respect, the prevalence of sustainable cross-neutralizing antibody levels to non-vaccine HPV types is significantly higher in bivalent vaccine recipients (3-dose) as compared to quadrivalent vaccine recipients (3-dose) followed by the Finnish Maternity Cohort for up to 12 years post-vaccination.[10] Importantly, neutralizing antibody levels to alpha-9 HPV types and reported vaccine efficacy against corresponding persistent infection were significantly correlated in bivalent vaccine recipients, but (as expected) not in quadrivalent vaccine recipients. Nevertheless, long-term vaccine efficacy against cervical intraepithelial neoplasia caused by HPV16 and HPV18 remained very high for both bivalent and quadrivalent vaccines.[49–51]

Clinical data suggest that the mechanisms of cross-type protection are predominantly driven by cross-neutralizing antibodies. On the other hand, it may also depend on the activation of antibody-mediated innate immune responses (therefore beyond virus neutralization). Roy et al[52] recently demonstrated significant differences in Fc-effector functions following bivalent and quadrivalent HPV vaccination, with the first one triggering an enhanced coordinated response against HPV16 and HPV18 in terms of antibody subclass, isotype, Fc-receptor binding and Fc-effector functions as compared to the latter one. We need to understand how these findings explain differences in the observed cross-protective efficacies induced by the bivalent and quadrivalent vaccines, and their relevance for the immune responses induced by nonavalent vaccines.

The steady antibody responses induced by the HPV vaccines are a result of sustained production by plasma cells, largely afforded through the generation and maintenance of strong memory B cell activation. HPV-specific memory B cell responses are induced early upon vaccination[53] and may remain quiescent for long periods until readily recalled following antigen (re)exposure. Sustained immune responses induced upon vaccination are critically impacted by the number and timing of vaccine doses, but pertinent data on the effect of doses in HPV vaccine-induced B-cell response is currently scarse and challenging to interpret due to discrepancies in cohort ages[54] despite the strong evidence supporting an optimal memory B cell response in children aged 9–13 years.[55] Memory B cell response triggered after infection may be a key mechanism driving vaccine-induced protection following 1-dose schedule but this and associated caveats remain to be elaborated.

7 | RESILIENCE OF HPV VACCINATION PROGRAMS

7.1 | Context and threats

Disease prevention and control programs worldwide have regularly suffered from severe disruption caused by factors such as changes in

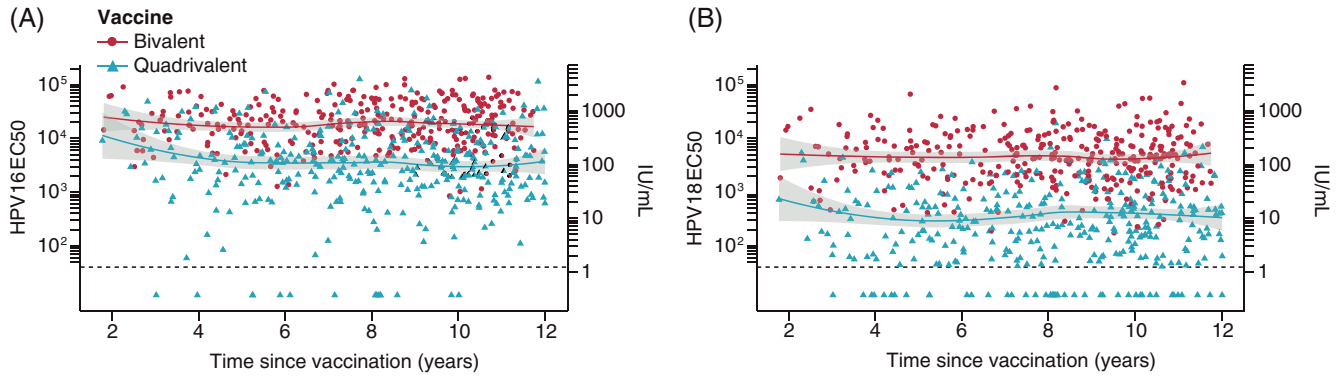

FIGURE 3 Sustained neutralizing antibody levels to HPV16 (A) and HPV18 (B) induced by the bivalent and quadrivalent HPV vaccines in women followed up by the Finnish Maternity Cohort for up to 12 years. Each data point represents the individual neutralizing antibody titers (EC50) calculated by a high-throughput pseudovirion-based neutralization assay, with corresponding locally estimated regression lines. Dashes lines indicate the assay cut-off value. Note the corresponding IU/mLs of neutralizing antibodies shown in the second *y*-axis. Adapted from Mariz et al.[6]

political commitment, financial constraints, skepticism of the civil society, geo-political unrest, and environmental disasters. The most recent episode of massive and global disruption of healthcare systems was caused by the COVID-19 pandemic.[56] The pandemic has disrupted the Global Strategy for cervical cancer elimination.[57] With respect to HPV vaccination, the pandemic slowed down or interrupted vaccine delivery where HPV vaccination programs were already active, delayed the launch of HPV vaccination programs in several resource-limited countries, and limited the production of HPV vaccines to favor the manufacturing of other vaccines.

7.2 | Threat mitigation: Building up resilience

To mitigate the negative impact on health of such public health crises as well as the waste of human, logistic, and financial resources, it would be farsighted to devise and implement pre-emptive measures aimed at improving the resilience of public health programs. In two separate modeling studies conducted in Sweden[12] and India,[58] respectively, we have assessed the potential mitigation effect offered by gender-neutral vaccination. In the former study, conducted before the coronavirus pandemic, and using a population-based HPV transmission model adapted to account for Swedish HPV epidemiology and sexual behavior, we have illustrated how the addition of boys' vaccination to an ongoing program targeting girls only can make an HPV vaccination program more resilient to sudden and prolonged vaccination interruptions. Resilience is defined, for both gender-neutral and girls-only HPV vaccination, as the residual impact of HPV vaccination in case of a temporary coverage reduction. In the latter study, conducted after the coronavirus pandemic, and using an agent-based HPV transmission model adapted to the Indian setting, we have illustrated how gender-neutral vaccination remains more resilient than girls-only vaccination over a wide variation of duration and magnitude of the disruption of the vaccination program.

The condition underlying the gain in resilience by switching from girls-only to gender-neutral vaccination is the age difference between sexual partners, with men being on average older than women within sexual partnerships almost everywhere worldwide.[59] In cases of vaccination disruption, the birth cohorts of boys vaccinated before the disruption would indirectly protect the cohorts of younger girls who missed out on vaccination during the disruption period.

7.3 | Generalization and considerations

As illustrated with our above-mentioned studies, which were conducted in populations with substantially different demographic and sexual behaviors, the gain in resilience attributable to gender-neutral vaccination is generalizable to any settings in which men tend to be older than their female partners. Of note, here we have considered gender-neutral HPV vaccination only as an approach to mitigate the pernicious impact of vaccination disruption. However, including boys as a target of HPV vaccination programs has advantages also in absence of disruption as this approach offers a direct protection to males against cancers attributable to HPV infection and an indirect protection to unvaccinated women against cervical cancer and other HPV-related cancers. Currently, WHO do not actively recommend vaccination of boys. Currently the main impediment to the introduction of gender-neutral vaccination is vaccine availability and cost.

8 | COST-EFFECTIVE CERVICAL CANCER SCREENING IN HPV VACCINATED BIRTH COHORTS—A GENERAL PICTURE

We simulated cervical cancer-related disease burden in HPV-vaccinated birth cohorts under various screening and vaccination scenarios. In particular, annual quality assured life-years lost and treatment costs due to cervical cancer and screening findings,

including follow-up, as well as costs of screening tests were simulated in a population consisting of 50,000 boys and 50,000 girls birth cohorts using multitype HPV transmission and progression models[60,61] which were adjusted and calibrated to prevaccination era data.[62,63] In the post-vaccination steady state, the annual disease burden equals the lifetime (un-discounted) disease burden among all birth cohorts including (also unvaccinated cohorts), but except for HPV16 the steady state is achieved among vaccination-age birth cohorts in a few birth-cohorts (Table 1) compared to the decades for the total population.

The vaccination scenarios were no vaccination, girls-only vaccination, and girls-and-boys vaccination, using bivalent, quadrivalent, or nonavalent vaccines with 80% coverage. The screening scenarios were no screening, actual prevaccination era screening (in Finland), and 38 screening scenarios. The 38 scenarios are not specified here as the purpose was not to compare different specific screening scenarios but to present a general picture. Among the 38 screening scenarios, the least intensive one consisted of two lifetime screening rounds at ages 35 and 50 years.

According to the simulation, screening did remarkably well to reduce quality-assured life-years lost in the prevaccination era (Figure 4, black X vs circle), although the actual prevaccination era screening was not optimal, especially regarding the costs. The cost-effectiveness analyses to start vaccination programs were typically assuming no changes in the screening programs (Figure 4B, comparison between x's), but the continuation of actual prevaccination era screening is extremely costly compared to the other screening scenarios (x's vs dots). Vaccination alone had a huge impact on the disease burden (Figure 4B), however, except for the most effective vaccination programs, some screening is needed also in vaccinated populations to achieve the realized level of quality-assured life years lost at prevaccination era. While the lightest screening scenarios (Figure 4B, right-most dots) reduce the disease burden with at most low increase of costs compared to the no screening scenario with all vaccination programs, improving the lightest screening scenarios differs remarkably between the vaccination programs. For the lower effectiveness vaccination programs (eg, girls-only programs), there is room for cost-effective improvements as many scenarios exist with lower quality-assured life years lost and only moderately increased costs. For the higher effectiveness vaccination programs (boys-and-girls programs using vaccines with wide type-specific protection), improving the lightest screening scenarios is more difficult as the costs increase steeply compared to pertinent improvements. Eventually success of the vaccination program must be considered in design

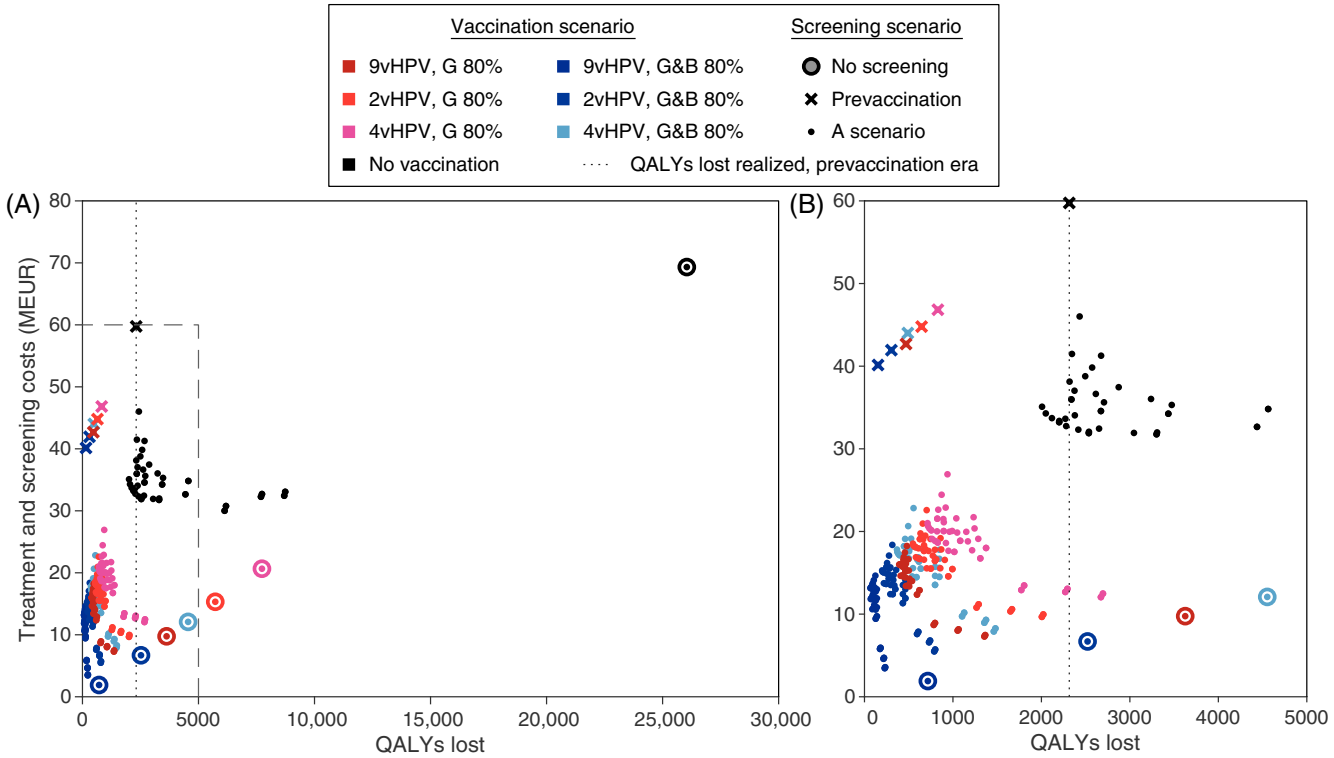

FIGURE 4 Annual cervical cancer-related disease burden (QALYs lost, *x*-axis). Costs of cervical cancer screening and treatment of all screening findings and their follow-up as well as of cervical cancer detected by symptoms (*y*-axis) in a population consisting of 50.000 + 50.000 birth cohorts under various vaccination and screening scenarios, in their (new) steady states in Finland. The dashed area in panel A is zoomed and presented in the panel B. Each marker corresponds to a scenario. Colors are for vaccination scenarios using nonavalent, bivalent or quadrivalent vaccines with 80% coverage or no vaccination (black, no vaccination; reddish, girls-only vaccination; bluish, girls-and-boys vaccination). Marker styles represent different screening scenarios: circle is for no screening, x is for the actual prevaccination era screening, and dots are for the other 38 (non-specified) screening scenarios. The vertical dot line shows the realized level of QALYs lost on the prevaccination era.

of a cost-effective screening program for vaccinated birth cohorts. The vaccinated birth cohorts are currently entering the traditional screening ages, indicating an urgent need for updating the programs to avoid high costs and adverse consequences of screening.

8.1 | Disclaimer

Even though the two round screening scenario was attractive among the analyzed scenarios, we are not claiming that such program should be implemented based on this analysis. Results of a randomized trial on frequent (at ages 22, 25 and 28) vs infrequent (at age 28) screening of 7000 women, who received HPV vaccination at age 14 between 2007 and 2009[64] are emerging later this year, and should help to establish an optimal scenario.

9 | CONCLUSIONS

The discovery that several common forms of cancer are caused by an infection that can be easily prevented using effective vaccines is the most important medical intervention for cancer prevention that exists today. The experience from Covid vaccination efforts have clearly demonstrated that also very large-scale global efforts with massive number of vaccinations can be achieved in a short time and massive numbers of vaccine doses can be produced, when there is sufficient motivation to do so. The scientific evidence reviewed at the workshop suggested that strategies with more ambitious use of HPV vaccines would be helpful to accelerate elimination of HPV and cervical cancer.

It is also evident that the huge scientific advances in the HPV field for example in etiological research and for generating highly effective HPV vaccines and HPV screening tests are not enough to automatically result in rapid elimination of HPV and cervical cancer. Accelerated elimination will need sound evidence basis from continued and updated research efforts, both in basic sciences, in vaccine research and translational sciences.

AUTHOR CONTRIBUTIONS

Matti Lehtinen: Introduction. **Laia Bruni:** Worldwide HPV vaccination and screening coverage. **Miriam Elfström:** Faster elimination of cervical cancer by combining HPV vaccination and screening. **Penelope Gray:** Generation and impact of herd effect against human papillomavirus. **Margaret Logel:** Ethical issues related to HPV vaccination policy. **Filipe Colaço Mariz:** Sustainability of HPV vaccine-induced protective antibodies. **Iacopo Baussano:** Sustainability of HPV vaccination induced overall protective effectiveness. **Simopekka Vänskä:** Cost-efficiency of combined HPV vaccination and screening. **Joakim Dillner:** Editing, Abstract and Conclusions. **Eduardo Franco:** Editing, Abstract and Conclusions. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors do not have a conflict of interest to declare, but over the years Eduardo Franco has served as occasional consultant to companies involved with HPV vaccines (Merck, GSK) or HPV diagnostics (Roche, BD). The Cancer Epidemiology Research Program (with which Laia Bruni is affiliated) has received unrestricted research grants from Merck, and HPV test kits at no cost from Roche for research purposes.

DATA AVAILABILITY STATEMENT

Requests concerning data availability need to be addressed to co-authors responsible for a given chapter as indicated at the end of the report.

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