OPINION

HPV-FASTER: broadening the scope for prevention of HPV-related cancer

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Abstract | Human papillomavirus (HPV)-related screening technologies and HPV vaccination offer enormous potential for cancer prevention, notably prevention of cervical cancer. The effectiveness of these approaches is, however, suboptimal owing to limited implementation of screening programmes and restricted indications for HPV vaccination. Trials of HPV vaccination in women aged up to 55 years have shown almost 90% protection from cervical precancer caused by HPV16/18 among HPV16/18-DNA-negative women. We propose extending routine vaccination programmes to women of up to 30 years of age (and to the 45–50-year age groups in some settings), paired with at least one HPV-screening test at age 30 years or older. Expanding the indications for HPV vaccination and much greater use of HPV testing in screening programmes has the potential to accelerate the decline in cervical cancer incidence. Such a combined protocol would represent an attractive approach for many health-care systems, in particular, countries in Central and Eastern Europe, Latin America, Asia, and some more-developed parts of Africa. The role of vaccination in women aged >30 years and the optimal number of HPV-screening tests required in vaccinated women remain important research issues. Cost-effectiveness models will help determine the optimal combination of HPV vaccination and screening in public health programmes, and to estimate the effects of such approaches in different populations.

Human papillomavirus (HPV) has been clearly established as a cause of human cancer. Estimates have been generated of HPV-attributable fractions for cancers of the cervix, vulva and vagina in women, of the penis in men, and of the anus and oropharynx in both sexes, and range from almost 100% for cervical cancers to 20–40% for cancers of the oropharynx[1–5]. HPV types 16 and 18 (HPV16/18) are the most important cancer-related HPV genotypes, and make the greatest contribution to the cancer risk attributable to this virus; these high-risk types account for 70% of all cervical cancers and 80% of HPV-positive anal and oropharyngeal cancers[6,7]. Two additional low-risk HPV types, HPV6 and HPV11, are responsible for the great majority of anogenital warts, laryngeal papillomatosis (benign tumours in this upper respiratory tract), and a small proportion of anogenital cancers[8]. Quantitative estimates attribute at least 610,000 cancer cases and 320 million cases of anogenital warts worldwide annually to HPV[6,9,10].

Cervical cancer is the third most-common cancer in women worldwide, based on age-standardized rates, and remains the commonest cancer affecting females in 41 (22%) of 184 countries[11] — mainly those in developing regions, although it was once the most-common cancer in women from developed regions[12]. The disease has a relatively early age at onset and ranks among the three most-frequent cancers in women aged <45 years in 82% of countries[11]. The cervical cancer incidence has been greatly reduced in the populations of many developed countries that have made substantial investments to provide wide screening coverage and the associated infrastructure required to diagnose and treat precursor lesions in women with a positive screen[13,14]. These programmes, however, are costly and are not devoid of negative adverse effects related to overdiagnosis and overtreatment of cervical neoplasms that have a very low potential for progression to cancer[15–18]. Surgical treatment of screen-detected cervical lesions in young women also carries some obstetric risks, including increased frequencies of premature births and global perinatal mortality[19] — although the latter is only firmly established for extensive cold-knife conization of cervical neoplasms.

Prevention of cervical cancer

Two approaches exist for controlling cervical cancer incidence: secondary prevention using cytology and/or HPV tests to screen for cervical cancer precursors, with subsequent colposcopy and treatment if needed; and primary prevention via HPV vaccination. Within the following sections, some of the conceptual differences between these approaches are discussed. Other less-established screening methods (such as visual inspection and the use of novel biomarkers) is beyond the scope of this article[20].

Cervical screening

Where offered broadly in organized public-health programmes, the Papanicolaou smear test (commonly known as the Pap smear), and refinements of this methodology through liquid-based cytology and computer-assisted reading, has achieved large reductions in cervical cancer incidence and mortality

Table 1 | **Summary of the sensitivity and specificity of primary cervical cancer screening methods***

Screening test	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)
Detection of CIN2+			
Cytology (ASC-US+)	25	70.0% (62.5–77.6%)	91.9% (90.3–93.6%)
HC2	31	90.4% (88.0–92.8%)	88.5% (87.0–90.0%)
Cytology (ASC-US+) and HC2 (co-testing)	13	94.2% (90.8–97.6%)	87.7% (85.0–90.3%)
Detection of CIN3+			
Cytology (ASC-US+)	21	74.6% (65.6–83.6%)	91.8% (90.0–93.7%)
HC2	22	95.3% (93.3–97.3%)	89.0% (87.2–90.8%)
Cytology (ASC-US+) and HC2 (co-testing)	12	96.7% (93.7–99.7%)	82.9% (77.1–88.6%)

*Updated meta-analysis data based on data from studies by Arbyn *et al.*[21,22] Abbreviations: ASC-US+, atypical squamous cells of undetermined significance or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; CIN3+, cervical intraepithelial neoplasia grade 3 or higher; HC2, Hybrid Capture® 2 High-Risk human papillomavirus DNA Test™; No., number.

— particularly in countries with a high target-population coverage, coupled with quality assurance and quality-control activities embedded within the programme[13,14]. One of the limitations of cytology-based screening is the relatively low sensitivity for detecting precursor lesions of cervical cancer (cervical intraepithelial neoplasia grade 2 or higher (CIN2+)) compared with that of HPV testing[21,22], necessitating repeated screening at short intervals. The complex logistics and health-care infrastructure required to implement quality control for the intrinsically subjective nature of cytology and to carry out adequate clinical management of women with a positive screen is a further limitation. For these reasons, cervical cytology screening has not been successfully implemented in most developing countries, where screening tends to be opportunistic, unorganized, and selective for individuals from high socioeconomic classes in urban areas, resulting in minimal or no reduction in cancer incidence or mortality[23].

Applying molecular technologies to screen for the causative agent of cervical cancer, HPV, was first proposed in the early 1990s[24,25]. The results from subsequent randomized trials and cohort studies have consistently demonstrated that HPV testing can be used to achieve a 30–40% gain in sensitivity for detecting precursor lesions (both CIN2+ and CIN grade ≥3 (CIN3+); TABLE 1), compared with cytology, at the cost of a 3–5% loss in specificity; larger gains in sensitivity are seen when longitudinal outcomes are considered[21,22,26]. For example, an updated meta-analysis study reported that the sensitivity of a single HPV-DNA test event — in this case, using the most established Hybrid Capture® 2 (HC2) HighiRisk HPV DNA Test™ (QIAGEN, Netherlands)—for detection of CIN2+ was 90% and was 95% for CIN3+, compared with 70% and 74%, respectively, for high-quality cytology[27]. Randomized controlled trials showed that HPV testing not only detects more precursor lesions at first screening, but also leads to an overall reduction in the incidence of these lesions in the following years among the screened population[28–31], as well as a substantial 70% reduction in subsequent cases of invasive cervical cancer[26]. An important consequence of the higher sensitivity of HPV testing, compared with cytology, for detecting CIN2+ is the longer duration of a low-risk period after a negative result, both for high-grade CIN and invasive cancer[26], enabling safe extension of the intervals between screening episodes.

An additional advantage of cervical screening by HPV testing is the objective, reproducible nature of the test, whereas cytology — even in expert hands — has an intrinsic subjective component that results in substantial inter-reader discordance[32]. In addition, the development of semiautomated HPV-testing platforms has led to the creation of high-throughput systems, which further reduce the test variability through uniform sample handling[32]. Thus, this approach will be particularly important in the future when screening vaccinated women: the frequency of abnormal cytology will probably be 50–80% lower than current rates, which will pose additional quality-control problems (such as overcalling of minimal cytological changes) in terms of maintaining the attention of cytologists when viewing slides that are predominantly (95–98%) normal[33].

Reviews published in the past 3 years have concluded that HPV-based technologies could be used for primary screening[21,34,35], and several guidelines currently recommend HPV testing for primary screening[22,36–40]. Clinically validated tests include the HC2 HPV DNA Test™ and the GP5+/GP6+ PCR–enzyme immunoassay, although other HPV tests show equivalent accuracy and could also be used as stand-alone primary screening tests[35]. In the USA, the HC2 HPV DNA Test™, Cervista® (Hologic, USA), APTIMA® (Hologic, USA), and the cobas® HPV test (Roche Molecular Systems, USA) are approved by the FDA in combination with cytology, but only the cobas® HPV test is also approved as a stand-alone screening test[41].

Nevertheless, the lower specificity of HPV testing for underlying CIN2+ than that of cytology poses problems that require further attention. This issue is particularly relevant in younger women: up to 20% of women aged less than 30–35 years can be HPV-positive without having CIN2+, although the proportion reduces substantially with age, to about 6% in women aged 35–49 years and 5% in those aged >50 years[22,42]. Thus, when HPV testing is the primary cervical screening modality, a second level triage step is necessary; cytology provides one option for secondary screening, but its low sensitivity will continue to necessitate short-term retesting. In addition, the low positive predictive value of low-grade cytological abnormalities, even in HPV-positive women, will still lead to over-referral of women without precancer or cancer for colposcopy. The use of molecular technologies will probably have an important contribution in this setting, but these tests will add to the complexity and the costs of the screening programme. At present, several candidate tests for triage of HPV-positive women are under evaluation, including slide assessment using

immunochemistry for the tumour-suppressor protein $p16^{INK4A}$ (also known as cyclin-dependent kinase inhibitor 2A) that is overexpressed in most HPV-related high-grade precursors lesions and invasive cervical lesions, particularly with dual staining of the cell-proliferation marker Ki67[43–45]; viral genotyping for detection of HPV16 and HPV18, or HPV16 and HPV18/45[46]; and the use of methylation markers[47]. Other biomarkers (such as viral load[48] and more-complete HPV genotyping[49]) might also have some value for triaging HPV-positive women, but currently none of these markers has been fully validated.

In order to be fully effective at a population level, to minimize undesired effects associated with lack of follow-up assessment, and to be sustainable, screening initiatives need the infrastructure and organization of publically funded, coordinated and centralized programmes. Where feasible, such programmes require a comprehensive diagnostic and treatment network of specialized colposcopy clinics to ensure good coverage and proper management of women with a positive screen. To ensure that a large proportion of adult women in a given population benefit from screening, population call and recall procedures are desirable. In addition, the system needs to integrate measures for maintaining quality control, and provide regular training and supervision. Systematic audits of the programme, notably for the invasive cancer cases that occur within the screened population, are also needed. When this level of infrastructure cannot be provided, single-screen campaigns can be effective, as has been shown in a large study in rural areas in India, in which one round of HPV testing was the only screening option of those evaluated that was shown to reduce cervical cancer mortality[50,51]; however, a high-quality screening test needs to be made available for a wide cross-section of the population, and adequate colposcopy and short-term follow up of women testing positive at screening must be provided, as must treatment for those needing it.

Departures from these principles has been shown to result in inefficient and expensive efforts, often resulting in over diagnosis, overtreatment and marked inequalities across socioeconomic strata[15,17]. Also the costs of screening can be unnecessarily high if a substantial amount of opportunistic screening activity coexists with the broader organized programme[16]. Irrespective of the specific strategy or test used, participation in screening activities has the inherent risk of overtreatment of nonprogressive lesions[19,52], and the psychological stress related to a positive screen result[53–55].

In recent years, the prices of HPV tests have decreased substantially, owing to greater utilization of and competition between products. Nevertheless, the logistics and the technology requirements for their successful deployment remain barriers to introduction and sustainability of cervical screening in low-income countries. To make screening more-efficient worldwide, it is necessary to validate novel technologies that build on the primary HPV-screening paradigm, and are suitable for use in settings with limited resources and manpower qualification, such as careHPV™ (QIAGEN, Netherlands), Xpert® HPV (Cepheid, USA), and other point-of-care HPV-detection methods. Other examples include cervical specimen self-sampling, urine-based tests, and newer molecular triage methods, including methylation analysis and p16–Ki67 dual testing[20,56–60]. Indeed, in combination with cryotherapy or similar 'low-tech' treatment procedures, these novel HPV-based technologies might make 'screen and treat' programmes viable in places where the health-care infrastructure is unavailable or inadequate to support the current population-wide screening protocols.

HPV vaccines

At present three prophylactic HPV vaccines are licenced: the tetravalent (4vHPV) vaccine Gardasil® (Merck & Co., USA/Sanofi Pasteur MSD, France), known as Silgard® in some regions, which is based on virus-like-particle (VLP) antigens for HPV types 6, 11, 16, and 18; the bivalent (2vHPV) vaccine Cervarix® (GlaxoSmithKline, UK), which is based on VLP antigens for HPV16 and HPV18 only; and Gardasil 9® (Merck & Co., USA), a nonavalent (9vHPV) vaccine based on VLP antigens for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Two of these vaccines (4vHPV and 2vHPV) have been extensively evaluated in phase III and phase IV trials, and many excellent reviews on vaccine efficacy and safety of these agents are available in this journal and elsewhere[61–63].

Following the first approval of an HPV vaccine in 2006[64], population-based post-marketing studies have confirmed that within 5 years of introduction of the HPV vaccine, substantial reductions can be achieved with regard to the prevalence of cervical, vulvar, vaginal, anal, and oral infections by the HPV types included in the vaccines; precancerous cervical lesions; and genital warts if 4vHPV is used[62,65–70]. In addition, a marked 'herd-protection effect' has been seen in populations with high background HPV-vaccination coverage, whereby reductions in the rates of infection and cervical neoplastic disease have been observed not only among those women who received the vaccine, but also among the nonvaccinated females and males aged <25 years[66,71]. The safety of the available HPV vaccines has also been clearly established[63].

The first-generation commercially available vaccines included HPV16/18 VLPs and directly protect against these two HPV types, which cause 50% of CIN2+ and 70% of invasive cervical cancers[1,72]. In late 2014, the 9vHPV vaccine was first licenced in the USA[73]. This vaccine includes VLP antigens for five other high-risk HPV types (HPV31/33/45/52/58) in addition to those in the 4vHPV vaccine, and has so far been evaluated only in phase III trials[69]. The first published results for the 9vHPV vaccine are, however, promising: the same protection efficacy against the four HPV types included in the 4vHPV vaccine was demonstrated; a high degree of protection (>95%) against infections and high-grade anogenital lesions caused by the five additional HPV types represented in the 9vHPV vaccine was seen, compared with women who received the 4vHPV vaccine; and a very good safety profile was observed[69]. On the basis of the comparable antibody responses observed for the 9vHPV vaccine and the 4vHPV vaccine, a similar degree of long-term protection is assumed[74]. Use of the 9vHPV vaccine would increase the estimated preventable fraction of cervical cancer from 70% to 90%, and from 50% to 80% for pre-invasive cervical neoplasia. Of note, a similar avoidable fraction of CIN3+ to that of the 9vHPV vaccine (vaccine efficacy in women with no evidence of oncogenic HPV infection at baseline: 93.2%,95% CI 78.9–98.7%) might also be achievable with the 2vHPV vaccine if the early evidence of broader cross-protection against HPV types other than HPV16/18 reported at 4-year follow up of a phase III trial is reflected in population studies with long-term follow up[75–77]. The 4vHPV vaccine has also been demonstrated to provide considerable cross-protection,

but only significantly against HPV31[62,77], which accounts for only ~4% of cervical cancer cases[1].

Indications for HPV vaccination

Compared with secondary prevention of cervical cancer through screening, primary prevention through HPV vaccination has three intrinsic advantages. Firstly, owing to the predicted long-term protection achieved after a three-dose course of the vaccine[78,79], fewer intervention visits will be required — currently two clinic visits with at least a 6-month interval for girls ≤14 years of age and three visits within 12 months for women aged ≥15 years to receive the vaccine are needed. Secondly, when a high fraction of individuals in a population receive the vaccine, vaccination creates the aforementioned herd-protection effect by reducing the fraction of susceptible individuals, thus interrupting HPV transmission in the community. Thirdly, HPV vaccines have the potential to protect against all forms of HPV-induced cancer-precursor lesions and invasive cancers, whereas screening only protects against cervical cancer.

Since the first licensing of the 4vHPV vaccine in 2006 by the FDA in the USA[64], the early limited indications for the use of HPV vaccines in females up to the age of 26 years[80] have been challenged by new knowledge of very high efficacy in boys and older women[81–84], particularly in light of the substantial reduction in vaccine costs. Many national advisory boards, however, continue to make recommendations based on the early knowledge[63], thus under-exploiting the potential benefit to be gained from wider use of the vaccines on the basis of knowledge obtained in recent years.

In 2005–2006, the rationale for HPV vaccination was based on a restricted set of terms of reference: the target was cervical cancer, therefore, vaccination was only indicated for women; the focus for HPV vaccination were adolescents before sexual debut to avoid vaccinating women previously exposed to the virus, which in some instances prompted the misinterpretation that sexually active women, irrespective of previous exposure to the virus, would not benefit from vaccination; and prevention was restricted to HPV16/18-related disease, creating the notion of a partial vaccine against HPV-related cancer. In addition, the initial costs of the vaccines were very high and most national indications were strongly influenced by local budgetary constraints. Models of cost-effectiveness and thus early regulations were all framed by these principles, and as a consequence, very limited indications of use were recommended and adopted in terms of the sex and age groups of individuals targeted by public programmes[85]. For example, many countries initiated vaccination of single cohorts of girls (mostly in the age range of 11 to 14 years), and extended age range catch-up programmes were offered in only a few countries, notably Australia and Denmark, where women up to the age of 26 years were offered vaccination[86,87]. The limited implementation of catch-up programmes was further explained by the costs, logistics, and necessary efforts required to extend the age range and the gender-neutral indication of HPV vaccination.

Interestingly, none of the early recommendations explicitly addressed the implications that universal HPV vaccination of adolescent girls would have on cervical screening programmes when the vaccinated cohorts reached the age of eligibility for initiation of screening. However, several subsequent studies noted the importance of and cost savings associated with introducing less frequent primary HPV-screening in place of cytology in vaccinated cohorts, owing to the much lower CIN2+ rates and resulting decrease in the positive predictive value of screening[88,89]. In addition to this reduction in the incidence of underlying disease of interest, clear evidence exists that non-HPV16/18 type cervical lesions progress more slowly to CIN2+ and invasive cancer than HPV16/18 lesions[90,91]. This observation provides further rationale for the safety of extending the duration of the screening intervals in vaccinated women. The conventional screening protocols are clearly not cost-effective and need to be modified in vaccinated individuals[85,88], underlying the need for comprehensive programmes combining both vaccination and screening, in order that the screening interval for vaccinated women can be adjusted accordingly. The most appropriate screen intervals will need to be determined in randomized clinical trials, modelling studies, and through close monitoring of data from existing programmes.

The high costs of the vaccine during the initial years after approval further contributed to delaying their introduction in many developing nations. The recognition and approval of two-dose regimens (rather than three doses) among adolescents, and the agreement reached by the GAVI alliance (a public–private partnership committed to increasing access to vaccines) to include HPV vaccines in their portfolio — prompted by the low prices granted by the manufacturers — is an encouraging sign for rapid deployment of vaccination in the poorer regions of the world[92,93]. Thus, strategies that combine HPV vaccination with simplified protocols of HPV screening will be of interest in many emerging and developing populations in the foreseeable future.

The HPV-FASTER protocol

Rationale for the programme

HPV screening and vaccination are complementary preventive options often implemented as separate and noncoordinated programmes. The HPV-FASTER protocol, here described for the first time, aims to address this disconnect by combining both strategies with the ultimate purpose of accelerating the reduction of cervical cancer incidence and mortality. Uncertainties related to this strategy are further discussed in a separate section.

Results from two phase III trials comparing HPV vaccination against placebo among adult women (aged up to 45 years and 55 years for the 4vHPV and 2vHPV vaccines, respectively)[83,84], and the consistent results of HPV-screening trials[21,22,26] provide the basis for the HPV-FASTER proposal. The two vaccination trials reported results for different cohorts of women whose HPV and cytology status were measured at the time of vaccination (TABLE 2)[83,84]. Although the published nomenclature of the cohorts differs slightly between the trials, two broad groups of women can be identified. The first group comprised women who entered the 'per-protocol' or 'according-to-protocol' analyses of vaccine efficacy were defined as those who at study entry were: HPV16/18-DNA negative in cervical samples and serologically negative for HPV16/18 antibodies (an indirect marker of past infections); had normal or only low-grade cervical cytology abnormalities at baseline and at month 7 after the completion of the vaccination protocol; and received the three required vaccine doses at the specified timing of day 1, 1–2 months, and 6 months, and were without protocol violations. By contrast, the second group included all women in the 'intention-to-treat' or 'total-vaccinated-cohort' protocols

who received at least one dose of the HPV vaccine, irrespective of HPV status in serum or by cytology at study entry or at completion of the vaccination scheme. Trials of both the 4vHPV and 2vHPV vaccines confirmed that protection against infections — and their related outcomes (cervical precancer or cancer) — caused by vaccine-related HPV types was very high, provided that the women were HPV-DNA negative for the vaccine type at the time of vaccination; estimates of vaccine efficacy in the per-protocol groups were in the range of 85–90%, depending on the trial end points[83,84]. Reduced, but nonetheless important, vaccine efficacies of approximately 50% were calculated for the intention-to-treat cohorts[83,84]. Clearly, however, HPV-DNA-positive women did not show any evidence of protection against diseases related to HPV types that they tested positive for at the time of vaccination[94]. Thus, vaccination can offer protection to women without a current infection or disease, irrespective of previous viral exposure, and among those currently infected, can protect against further infections as well as re-infection with the same HPV type.

In accordance with these findings, the proposal of the HPV-FASTER protocol is to offer HPV vaccination to women in a broad age range of 9–45 years, or even 50 years in some settings, irrespective of HPV-infection status. Women of any age above 30 years, or even above 25 years would, in addition to the vaccination if aged less than 45–50 years, be screened using a validated HPV test as part of their initial visit; women who test HPV positive would be offered triage and follow-up diagnostic tests and treatment in accordance with recommended guidelines. FIGURE 1 provides a schematic representation of the HPV-FASTER concept and estimates of the potential for prevention of invasive disease, as reported for the different cohorts in the phase III vaccine and HPV-screening trials[21,22,26,83,84]. In terms of the protection offered by the vaccine, the effect of one round of HPV screening (with associated treatment) would be conceptually similar to transforming an 'intention-to-treat cohort' of adult women (with an expected vaccine efficacy of about 50% against lesions caused by the HPV types included in the vaccine) into a 'per-protocol cohort' of adult women (expected vaccine efficacy of about 85–90% for prevention of lesions attributable to HPV types included in the vaccine). Indeed, with adequate follow up and HPV vaccination, women who test positive for HPV at presentation for vaccination should have a very low risk, if any, of invasive disease. Because the sensitivity of HPV tests is not 100%, around 5–10% of the HPV-DNA-positive women will be misclassified as negative and will not benefit from triage and treatment, although the vaccination will offer them protection against the vaccine HPV types other than those that they are infected with at the time of vaccination.

The best data available from population studies in adult women that would resemble the HPV-FASTER proposal are the results of the vaccination programme in Australia that included women up to 26 years of age. The latest evaluation of this programme has clearly shown that the vaccine acceptability among this age group is high in the context

Table 2 | **Phase III HPV vaccination trials in women by HPV status at vaccination**[83,84,141]

Characteristic	4vHPV	2vHPV
Baseline characteristics of study population		
Number of women randomized*	Vaccine arm: 1,911 Control arm: 1,908	Vaccine arm: 2,881 Control arm: 2,871
Age range (years)	24–45	26–55
Proportion with current or past infection (vaccine HPV type)	33%	44%‡
Proportion testing HPV-DNA positive	HPV16 = 4.4%; HPV18 = 2.1%; HPV6 = 1.9%; HPV11 = 0.2%	HPV16 = 3.0%; HPV18 = 1.1%
Prevalence of HPV seropositivity	HPV6/11/16/18 = 29.8%	HPV16 = 29.5%; HPV18 = 27.3%
Outcomes in 'per-protocol'/'according-to-protocol' cohort§		
Persistent infection (≥6 months)‖	Cases: 9 (of 1,631) vs 85 (of 1,620)¶; **VE: 89.6% (95% CI 79.3–95.4)**	Cases: 6 (of 1,859) vs 34 (of 1,822); **VE: 82.9% (95% CI 53.8–95.1)**
CIN2+‖	Cases: 1 (of 1,631) vs 6 (of 1,620)¶; VE: 83.3% (95% CI −37.6–99.6)	Cases: 0 (of 1,898) vs 4 (of 1,854); VE: 100% (95% CI −100.7–100.0)
External genital lesions‖	Cases: 0 (of 1,631) vs 7 (of 1,620)¶; **VE: 100% (95% CI 30.8–100.0)**	NR
Outcomes in 'intention-to-treat'/'total-vaccinated-cohort' cohort#		
Persistent infection (≥6 month)‖	Cases: 110 (of 1,886) vs 211 (of 1,883)¶; **VE: 49.0% (95% CI 35.5–59.9)**	Cases: 71 (of 2,767) vs 132 (of 2,776); **VE: 47.0% (95% CI 25.4–62.7)‡**
CIN2+‖	Cases: 21 (of 1,886) vs 27 (of 1,883)¶; VE: 22.4% (95% CI −42.5–58.3)	Cases: 32 (of 2,740) vs 45 (of 2,737); VE: 29.1% (95% CI −22.5–59.6)‡
External genital lesions‖	Cases: 11 (of 1,886) vs 12 (of 1,883)¶; VE: 8.5% (95% CI −126.6–63.4)	NR
Outcomes in baseline seropositive, but HPV-DNA-negative women (those with previous infection)		
Persistent infection (≥6 month after at least 1 dose)‖	Cases: 5 (of 496) vs 15 (of 505); **VE: 66.8% (95% CI 3.8–90.5)**	NR
Persistent infection (≥6 month) or CIN1+ (after 3 doses)‖	NR	Cases: NR; **VE: 86.4% (30.1–99.0)**

*The women randomized include those subsequently excluded from analysis because of loss to follow up, consent withdrawal, or clinical adverse events, among others reasons. ‡Includes women with previous history of disease and HPV infection (~15%). §These women were negative for the HPV types targeted by the vaccine at baseline, based on HPV-DNA testing and serology, and received 3 doses of the vaccine. ‖Number of cases is reported in vaccine group vs control group, and VE data in bold indicates statistical significance. ¶Number of women at risk for each specific outcome was not provided in the last report of the 4vHPV trial, except for the number of seropositive women; thus, the numbers shown in this table were provided in a previous report[141] and refer to the total number of women by cohort — whether analyses used these numbers as denominators is unknown. #This cohort included women, irrespective of baseline HPV status, who received at least one dose of HPV vaccine. Abbreviations: 2vHPV, bivalent human papillomavirus vaccine (Cervarix®, GlaxoSmithKline, UK); 4vHPV, tetravalent human papillomavirus vaccine (Gardasil®/Silgard®, Merck & Co., USA/Sanofi Pasteur MSD, France); CI, confidence interval; CIN1+, cervical intraepithelial neoplasia grade 1 or higher; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; HPV, human papillomavirus; NR, not reported; VE, vaccine efficacy.

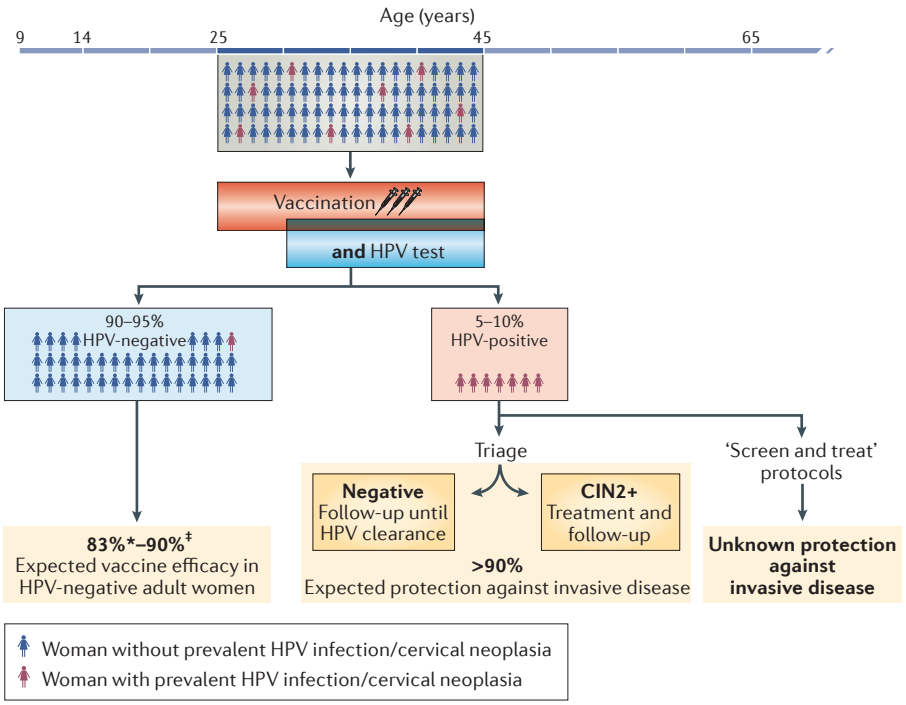

Figure 1 | **The HPV-FASTER core concept and the rationale for combined HPV screening and vaccination of women up to 45–50 years of age.** The HPV-FASTER strategy proposes to offer HPV vaccination to women aged 25–45 years, with concomitant HPV-DNA screening in women aged 30 years and above. In phase III clinical trials, HPV vaccination among women aged 25 to 45 or 55 years resulted in roughly 50% protection against cervical neoplasia[83,84]; however, the addition of an HPV-screening event, would predictably increase the expected protection as follows. Most of these women (90–95%) would test negative for HPV DNA[138], and the expected vaccine efficacy (*efficacy of 2vHPV vaccine; ‡efficacy of 4vHPV vaccine) in terms of prevention of 6-month persistent HPV infection, will be equivalent to the results of the 'per-protocol/total vaccinated–naive' cohorts in clinical trials (83–90%)[83,84]. Women who test positive for HPV-DNA (expected to be 5–10% in most populations), would receive additional triage (on the basis of HPV genotyping, cytology or other biomarkers), and diagnostic (colposcopy and biopsy) and treatment (conization) procedures, which should have a success rate close to 90% against disease recurrence and >90% for the reduction of mortality by cervical cancer, further accelerating the reduction in cervical cancer incidence[139,140]. Where diagnostic and treatment facilities are unavailable, 'screen and treat' alternatives, such as visual inspection with acetic acid and cryotherapy, could be performed, although the protection offered against cervical cancer mortality is at present unknown. As the sensitivity of the HPV-DNA test is not of 100%, failure to detect HPV-DNA in a small proportion of HPV-positive women (5–10% false negative rate[21,22]) will result in a group of individuals at high-risk of cervical cancer missed by the one HPV-screening test included in the HPV-FASTER campaign. Additional research will have to determine the required number of HPV-screening events in the vaccinated individuals and the optimal sensitivity of the HPV tests adopted, in order to maximize cervical cancer prevention. Likewise the updated results on HPV-vaccine studies, notably on efficacy, duration of protection, and spectrum of HPV genotypes covered, will significantly reshape the quantitative predictions for prevention of the future HPV-FASTER protocols. Abbreviations: 2vHPV, bivalent human papillomavirus vaccine (Cervarix®, GlaxoSmithKline, UK); 4vHPV, tetravalent human papillomavirus vaccine (Gardasil®/Silgard®, Merck & Co., USA/Sanofi Pasteur MSD, France); CIN2+, cervical intraepithelial neoplasia grade 2 or higher; HPV, human papillomavirus.

of a publically supported vaccination campaign[66]. Importantly, within 5 years after vaccination, dramatic reductions of HPV-type-specific prevalence, genital warts, and high-grade lesions were observed[66,95]. Furthermore, the protection against HPV infection was extended to nonvaccinated young females in the population, and boys in the population were protected both against HPV infection and genital warts[66]. These results strongly suggest that widespread vaccination of the population at the highest risk of HPV infection (individuals aged 15 to 30 years in most Western cultures) creates a protective environment in which HPV transmission is strongly reduced despite the multiple opportunities for sexual transmission of infection in most individuals.

In addition, male vaccination was introduced in Finland in 2007 as part of a large cluster randomized trial and in Australia in 2014 as a school-based government-funded programme aimed at further reducing HPV transmission and HPV attack rates[66,96]. The policy to vaccine females up to the age 26 years, coupled with generalized vaccination of boys, might lead to a detectable reduction in cervical cancer incidence in both countries within the next decade (that is, in women aged 26–36 years); such a result would provide a clear example for many other countries to follow. In addition, protection of both genders from other HPV-related cancers is likely, although this effect will take longer to manifest owing to the older average age at onset of these cancers.

One of the controversial issues for the HPV-FASTER strategy is whether to vaccinate women irrespective of HPV status or to restrict vaccination to only those who are HPV-DNA negative. This is because current HPV vaccines lack any therapeutic effect against the development of cervical lesions in women who are already HPV-DNA positive at the time of vaccination[94]. In favour of the nonselective approach, the evidence indicates that: vaccination of HPV-positive women or those with CIN2+ is safe; vaccination does not interfere with the treatment or follow-up of CIN2+ cases; it would be simpler logistically, and would facilitate compliance with three-dose vaccination regimens if the initial vaccine dose is delivered in combination with an HPV test in women aged ≥30 years; and vaccination would offer protection against infection and future disease caused by the other HPV types included in the vaccine that are not associated with the prevalent infection/lesion. One HPV-based screen after vaccination would capture most of the prevalent CIN2+ cases, and would signal a large proportion of the women who are likely to develop CIN2+ in the future (as indicated by HPV positivity) and thus require more-frequent follow up.

Further interest in vaccinating HPV-positive adult women (including women with a history of CIN2/3) comes from evidence that these women are at high lifetime risk of subsequent additional cancers of the anogenital tract[97]. In these patients, however, evidence remains to be generated as to the relative importance of new HPV infections, against which HPV vaccines would be protective, versus already prevalent or latent infections, against which

vaccination would have no effect. Trials exploring these alternatives might validate the use of HPV vaccines as part of the treatment of CIN2/3[98].

An alternative version of the HPV-FASTER protocol would consider vaccination of females aged 9 years to 45 years and offer HPV screening at any age above 30 years, but 1–5 years after vaccination rather than at the time of the vaccine first dose. Because of the protection against new infections offered by vaccination, any woman who tests positive for high-risk HPV at follow-up (at least 1 year after vaccination) would probably have a persistent HPV infection that was present at the time of vaccination and should, therefore, be followed up closely. In fact, it is of great importance for the effectiveness of the HPV-FASTER strategy to ensure that all women are HPV tested at least once after vaccination, as no protection is available against prevalent infections. Women who test negative for high-risk HPV types 1–5 years after vaccination with the 9vHPV vaccine, for example, plausibly have a very low risk, if any, of subsequent cervical cancer.

The third and most-conservative version of HPV-FASTER strategy would be to offer HPV screening and subsequent vaccination only to HPV-negative adult women aged up to 45 years. This form of the proposal would rely on the premise that adult women within this age group who test HPV-positive, when adequately triaged and treated, will be at a very low risk of invasive disease and, therefore, vaccination of these women would be unnecessary.

Implementation of the strategy

The context and the core scheme of the HPV-FASTER model is presented in FIG. 2. In addition, the existing cross-sectional HPV vaccination and cervical screening protocols used in most developed countries is illustrated (FIG. 2a). In existing schemes, one or more cohorts of girls are vaccinated, typically between 9–14 years of age, and variable levels of catch-up vaccination are undertaken — mostly in women aged up to 18 years, but with an upper limit of 26 years in Australia and Denmark. Commonly, women over the age of 25–30 years are offered screening, with cytology in most countries, but with a slow move towards HPV testing in Europe or a more-rapid implementation of co-testing with HPV and cytology in the USA. An important advantage of introducing HPV-based primary screening will be the reduction of

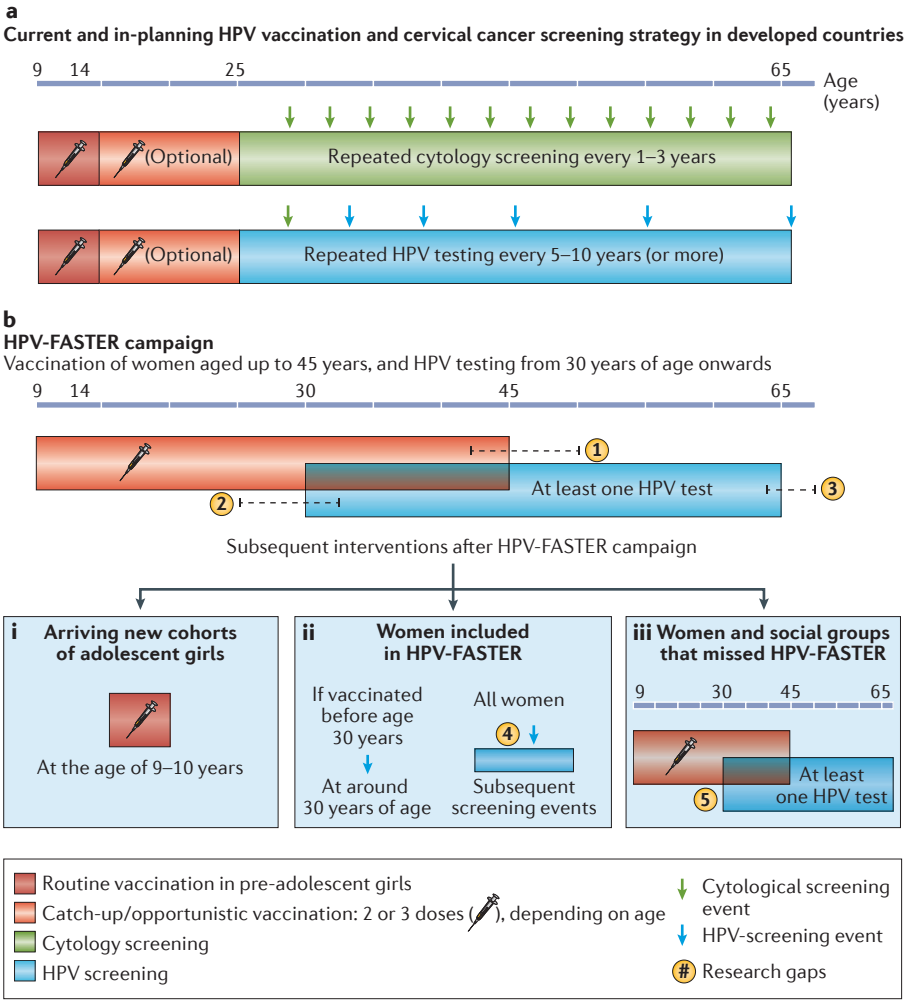

Figure 2 | **Framework of cervical cancer preventive strategies and of the HPV-FASTER strategy.** **a** | Current cervical cancer prevention model in most high-resource settings: organized immunization programmes targeting pre-adolescent girls; optional catch-up vaccination for women up to 26 years of age and subsequent screening with cytology (every 1 to 3 years) and/or HPV-DNA testing (every 3 to >5 years). Screening protocols for vaccinated women have not been established and, in the interim, standard cervical cancer screening protocols are typically offered irrespective of vaccination status. **b** | The HPV-FASTER campaign: HPV-FASTER proposes to expand HPV vaccination to women up to the age of 45 or 50 years (the exact upper age limit remains to be determined, as illustrated by research gap 1) paired with at least one HPV-DNA-based screening test performed in women aged 30 years and above (the exact age at first HPV screen is defined as research gap 2) up to age 65 (exact age at screening termination is defined as research gap 3). Women aged 30–45 years who have not been previously vaccinated are screened and vaccinated concomitantly. After the initial HPV-FASTER campaign, different interventions will still be required: **i** | routine HPV vaccination will continue for new cohorts of adolescent girls (that is, at age 9–10 years); **ii** | first HPV screening around age 30 for women vaccinated before this age during the HPV-FASTER campaign, in order to detect the prevalent HPV infections and related lesions that were likely already present at the time of vaccination. Subsequent HPV-screening needs (number of events and interval between screening events) of all women captured by the HPV-FASTER campaign remains to be determined (defined as research gap 4); and **iii** | at least one HPV-screening event with or without vaccination (defined as research gap 5) targeting those women not included in the HPV-FASTER campaign (including migrants and hard-to-reach social groups). It is understood that HPV-screening events need to be supported by disease management options (diagnostics and treatment or 'screen and treat' protocols), and that novel vaccines and diagnostic tools might dramatically expand on the potential of the HPV-FASTER concept. Likewise, HPV-FASTER strategies can be locally phased by initially expanding routine vaccinating to, for example, women aged up to 30 years (logistically the most consistent age group at which an informative screening event could be performed), whereas extension of the programme to women aged 45–50 years might require further support from additional studies on efficacy, cost-effectiveness and safety. Abbreviation: HPV, human papillomavirus.

the number of screening events required (that is, HPV testing every 5–10 years as opposed to Pap smears every 1–5 years). In general, cervical screening programmes have not yet incorporated different strategies according to vaccination status, except perhaps in Australia, where the need to change the primary screening technology to HPV testing for all women has been clearly established[99].

As introduced previously, the HPV-FASTER concept (FIG. 2b), proposes to offer, in a cross-sectional approach, a generalized HPV vaccination campaign aimed at girls and women aged 9 years to 45 years, paired with at least one HPV-screening test at any age above 30 years and eventual triage/diagnostic assessments among women who screen HPV positive (FIG. 1). FIGURE 2b also depicts the suggested longer-term continuation of the initial HPV-FASTER protocol, whereby maintenance of the adolescent vaccination programme continues with all new generations of 9-year-old girls (or whatever the designated starting vaccinating age is). The HPV-screening activity will remain at low intensity, with longer intervals between screens than in the current cervical screening programmes. In these circumstances, and if feasible, screening will remain more intensive for the pockets of nonvaccinated adult women, marginal social subgroups, and immigrant populations that might have missed routine vaccination. Thus, with the implementation of the HPV-FASTER proposal, the cervical cancer prevention model would evolve from the traditional 'repeated screening rounds' to a simplified 'screen and vaccine' strategy, followed by an yearly campaign of generalized HPV vaccination of girls aged 9–14 years.

Research and interventional scope

As part of the core HPV-FASTER scheme, several research issues need to be further investigated in order to optimize the strategy (FIG. 2b). In the early stages of the programme, these research questions will require the conduct of a few controlled trials in which women aged 25–50 years (or a similar age range) would be randomly assigned to receive either HPV screening alone, or HPV screening and HPV vaccination. The primary end points of these trials would be the longitudinal reductions in persistent HPV infections and high-grade cervical lesions. On the basis of such end points and with the help of models, the trials should answer a number of important questions. First, the ideal age at which the first HPV screening test should be offered, and particularly if HPV screening could be initiated at a later age in previously vaccinated women, especially those vaccinated at a very young age. Second, the upper age at which HPV vaccination would cease to be an attractive approach (whether to ages 30, 35 or 40 years, or above), after which point HPV screening would be the sole preventive option. Third, the appropriate age at which the last HPV screen would be offered (probably at 60–65 years of age). Fourth, the total number of subsequent HPV-screening events (likely in the range 1–3 events) and screening intervals (likely to be at least every 10–15 years, or possibly more than 15 years) required after vaccination of HPV-negative adult women, as a function of age at vaccination and the vaccine type used. In developing countries, a once-in-a-lifetime 'screen/treat and vaccinate' strategy might be adopted. Fifth, the optimal characteristics of the HPV-testing technology, such as the threshold of analytical and clinical sensitivity for HPV positivity, the time interval needed to deliver the results, validity with self-sampled specimens, and related costs. Finally, the programme should consider the local characteristics of the country and/or the population regarding the epidemiology of HPV and cancer burden, and well as considering the local resources and operational logistics.

Indeed, the optimal combined vaccination and screening programme will almost certainly be different in countries where no or minimal screening activities are currently in place compared with those where organized screening is well established, in which the new approaches (such as the HPV-FASTER proposal) must provide at least the same level of protection against cervical cancer as the existing ones. Countries with cervical cancer prevention programmes that are currently in the planning phases may wish to consider these concepts and review their plans; the priority of vaccinating and achieving high vaccine coverage among adolescent girls remains critical, although a major initial step forward would be to expand initial vaccination programmes from the restricted pre-adolescent age groups to include women up the ages at which HPV screening is considered acceptable (at age 25–30 years), and to offer one HPV screen at or above this age. Initially, this strategy would probably take the form of a demonstration programme in a geographically restricted population. Monitoring these limited cohorts would not only be highly informative as to the subsequent needs for screening, but would also proactively offer a very effective (and possibly cost-effective) alternative for lifelong protection against cervical neoplasia and for rapid reduction of the cervical cancer burden.

Uncertainties regarding HPV-FASTER

Some assumptions underlying in the HPV-FASTER proposal remain to be fully clarified. Firstly, whether HPV infections occurring after the age of 30 years are an important cause of cervical cancer on a population basis, notably if considered in the context of well-organized HPV-based screening programmes, is uncertain[90,100]. However, as cervical cancer rates remain high in women up to and beyond the age of 60 years in populations that have reasonable coverage by cytological screening, it seems probable that some of this disease burden is related to infections occurring after the age of 30 years[101]. The cancer cases with onset at older ages might also be caused by the reactivation of a latent infection[102,103], for which the benefit of HPV vaccination is currently unknown.

Secondly, whether women who have previously cleared an HPV infection occurring at a young age and therefore test HPV-DNA negative at the screening event are susceptible to new infections with either the same HPV type or other high-risk HPV types remains unclear[102]. All current evidence indicates that infections with different HPV types are independent, although women who have had one HPV infection are more likely to be exposed to other HPV types than women without prior infection[104,105]. If the benefit from the immune response generated by the 'primo' infection is sufficient to sustain protection against the same HPV type, vaccination of these women against these HPV types would be redundant. However, on the basis of data from clinical trials, in young-adult women, the protection from natural immunity is contingent to the antibody titres at baseline[106,107]; the antibody titres achieved by natural infection are greatly increased with subsequent vaccination[84]; previously infected women (that is, those who test seropositive but HPV-DNA negative at baseline) have an additional 65–85% protection against persistent infection and/or cervical intraepithelial neoplasia grade ≥1 after vaccination (TABLE 2); at present no validated

serological tests can discriminate those who remain susceptible from those who are protected; and protection from natural immunity against each of the seven high-risk HPV types included in the 9vHPV vaccine in the same woman is unlikely.

In addition to these uncertainties related to the natural history of the disease, adoption of the HPV-FASTER proposal will face a number of social and logistical challenges. From a social perspective, previous studies have shown a strong association of the self-perceived risk of new HPV infections and cervical cancer with willingness to undergo vaccination, which might be an important consideration regarding engagement of older women with the HPV-FASTER programme[108]. In developed countries, where 60–90% of adult women would agree to receive a HPV vaccine[109–111], women will be confronted by the choice between protocols comprising HPV vaccination and a reduced follow-up scheme or the current screening protocols that require screening visits at 1-year, 3-year, or 5-year intervals. This choice will be especially relevant in settings that have already introduced HPV-based primary screening, wherein a considerably reduced number of interventions are required. Ensuring continued participation in such limited-intervention screening programmes (for example, five HPV-screening events over a lifetime) might be a challenge following HPV vaccination, if the programme creates a false sense of complete protection. However, data from the USA indicated that 98% of vaccinated women under the age of 26 years intended to undergo cervical screening, and 95% of women aged 18–74 years were aware that vaccinated women should attend screening intervention[112].

Regarding logistics in developed countries, well-established screening algorithms will be difficult to change unless significant advantages and cost-effectiveness can be demonstrated. If vaccination registries are not integrated with the screening programme, partial vaccination of a population could create confusion as to the appropriate screening needs for any given individual. In developing countries, the sustainability of the vaccination campaign might be feasible only if the costs and logistics are facilitated by governments, international major agencies, such as GAVI, and by low vaccine prices. In addition, the HPV-screening component, and associated triage/treatment resources and facilities need to be sustainable locally. Unfortunately, alternative methods of low-cost cervical screening (such as visual inspection with acetic acid and others) have been shown not to be of sufficient efficacy to be adopted[20], and HPV-based screening programmes seem to be the only viable option. The HPV-FASTER strategy would be particularly suited to emerging economies with high incidence rates of cervical cancer and limited organized screening programmes, but with a reasonable clinical infrastructure (colposcopy referral clinics and laboratory facilities) and adequate vaccination programmes; this scenario would apply to most populations in Latin America[113,114], Central/Eastern Europe[115], and large populations in urban areas of Asia[115]. In other settings in which the provision of both a vaccination campaign and one round of HPV screening/treatment might be too costly and demanding to take on simultaneously as a government-funded strategy (for example, in some Sub-Saharan African countries), difficult decisions might need to be made as to which preventative measure should be introduced first. Other initiatives to reduce the HPV-related disease burden might be focused on increasing the vaccine uptake at younger ages and/or the vaccination of boys, although in these instances, the reduction of cervical cancer will occur at a much slower pace (TABLE 3).

Table 3 | **Key proposals for accelerated reduction of cervical cancer incidence**

Consideration	Developed countries	Developing countries
HPV vaccination	• Improve population coverage of HPV vaccination • Offer systematic HPV vaccination to adult women up to at least 30 years of age, and possibly up to ages 45–50 years	• Intensify the deployment of HPV vaccination worldwide • Large campaigns to offer HPV vaccination to females from the age of 9 years up to at least 30 years of age; vaccination to age 45–50 years could be considered, depending on the available resources
Screening	• HPV tests (with triage algorithms) should replace cytology as the primary screening option in women aged ≥30 years • Self-sampling methods and 'point-of-care' HPV tests could increase screening coverage • HPV-screening protocols would allow for a reduction in the number of screening events to 5–6 during each woman's lifetime	• During their lifetime, women aged ≥30 years should be offered at least one HPV-screening test, with appropriate subsequent triage and treatment options • Evaluate novel 'point-of-care' HPV-testing technologies • Self-sampling procedures should be evaluated
Integrated vaccination and screening	• Vaccination should enable further reduction of HPV-screening requirements • Maintain adapted screening programmes in vaccinated women	• Country/region-calibrated costs of vaccines and screening tests need to be negotiated to the highest possible degree
Research	• Accelerate trials and model the cost-effectiveness of increasing the number of vaccinated age cohorts in combination with different approaches to HPV screening and triage • Conduct trials of reduced HPV vaccine dosing (one-dose and two-dose regimens) in all age groups • Complete trials of vaccine efficacy in adult women with the 9vHPV vaccine • Complete longer-term evaluation of the cross protection conferred by 2vHPV • Monitor effectiveness of the HPV-FASTER protocols in a limited number of 'sentinel' countries	• HPV 'screen-and-treat' protocols need to be evaluated in the context of vaccination and HPV-screening programmes • Monitor effectiveness of the HPV-FASTER protocols in a limited number of 'sentinel' trials

Abbreviations: 2vHPV, bivalent human papillomavirus vaccine (Cervarix®, GlaxoSmithKline, UK); 9vHPV, nonavalent human papillomavirus vaccine (Gardasil 9®, Merck & Co., USA); HPV, human papillomavirus.

Modelling cost-effectiveness

Several studies have modelled the impact of adding a catch-up HPV-vaccination campaign aimed at post-adolescent girls and older women to the routine vaccination of pre-adolescent girls[116–131]. All of these studies concur that as age at vaccination

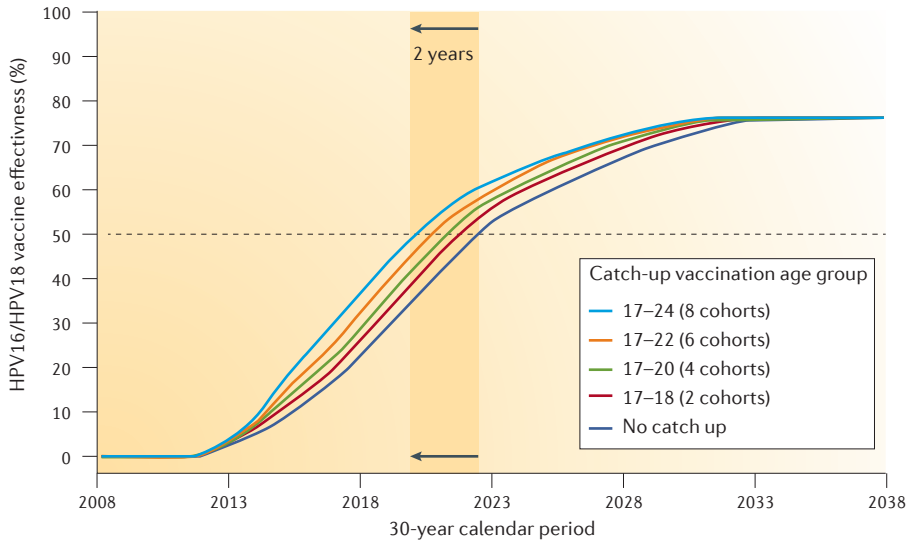

Figure 3 | **Modelling the effects of increasing the number of age cohorts vaccinated against HPV16/18 on time to reduction in the prevalence of HPV infection.** Baussano *et al.*[131] assessed the effectiveness of HPV16/18 vaccination, in terms of prevention of cervical HPV16/18 infections, among women aged ≤35 years, with catch-up vaccination of women aged 17–24 years. Using a mathematical model of HPV16/18 transmission and information on vaccination coverage among 11-year-old girls in an Italian population (65% coverage), the data were calculated based on the assumption of 50% vaccination coverage within the catch-up cohorts. Data were modelled for catch-up vaccination of women in four age groups, comprising between two and eight 1-year birth cohorts. Catch-up vaccination of an age group that spanned eight consecutive 1-year birth cohorts, encompassing women aged 17–24 years, was estimated to move forward by 2 years the time at which 50% vaccine effectiveness against HPV16/18 infection would be reached in the population. Abbreviation: HPV16/18, human papillomavirus types 16 and 18. Figure adapted from Baussano, I. *et al.* Upscaling human papillomavirus vaccination in high-income countries: impact assessment based on transmission model. *Infect. Agent. Cancer* **9**, 4 http://dx.doi.org/10.1186/1750-9378-9-4 (2014); © 2014 Baussano *et al.*; licensee BioMed Central Ltd, which was published under a Creative Commons Attribution License 2.0 Generic (CC BY 2.0; http://creativecommons.org/licenses/by/2.0/).

increases, the effectiveness and the cost-effectiveness of vaccination decrease, but some basic assumptions in these studies are rapidly becoming outdated as we accumulate evidence on the value of HPV screening, vaccination effectiveness and, more recently, on the value of the 9vHPV vaccine. Modelling the effectiveness of different screening intervals in vaccinated women depends largely on HPV-type-specific progression times from infection to invasion, for which available data are extremely sparse.

In terms of effectiveness, a model developed on the basis of data from France suggests that around 34% of deaths from invasive cervical cancer could be avoided by vaccinating all women aged up to 40 years[126]. The authors of a model calibrated to the situation in the Netherlands argue that a 50% reduction in cervical cancer incidence could be achieved by vaccinating women up to the of age of 25 years[125]. A key point brought out in some of the models is that a temporary catch-up campaign of older girls and younger women would advance by several years the impact of HPV vaccination on cancer reduction compared to vaccinating only adolescent girls. For developed countries, it has been estimated that a 1-year catch-up programme in eight birth cohorts of young women (that is, those aged 17–24 years) would accelerate the time to 50% reduction in HPV16/18 prevalence by between 2 years and 5 years depending on the country[130,131], as illustrated for Italy in FIG. 3. In terms of the cost-effectiveness of vaccination, all studies show the same decreasing pattern with age, but they are not consistent regarding the age at which vaccination is considered unattractive: some studies reported that the age limit for cost-effectiveness is 16 years[118,124,127], others 18–30 years[116,117,119,120,122,123,125,129], and others even to age 40 years[126,128].

One of the most-influential parameters that produces great variations in the cost-effectiveness ratios in all models is the price of the vaccine[118,120,125–127]. In recent years, vaccine prices have been reduced, mostly as a consequence of competition for the tender, but also pressure by international public health authorities[92,132,133]. Generally, the cost-effectiveness studies have considered a base price between €225 and €400 per three doses, which is substantially higher, by as much as 75%, than the obtainable price for national public health programmes. Westra *et al.*[125] varied their cost-effectiveness analysis across a range of vaccine prices from €45 to €125 per dose, concluding that HPV vaccination would be cost-effective only in 12-year-old girls with a vaccine price of €105 per dose, and would remain cost-effective for individual 1-year age cohorts up to an age of 30 years at a vaccine price of €45 per dose. Bogaards *et al.*[127] presented a reduction of the cost-effectiveness ratio of HPV vaccination for all 17–25-year-old women from €48,433 per quality-adjusted life year (QALY) to €9,572 per QALY when considering a 72% reduction in price (from €125 to €20), which would make vaccination of this age group very cost-effective.

These results suggest that HPV vaccination of women systematically to the age of 30 years — and possibly up to the ages of 45–50 years — at a sustainable price, paired with a limited number of HPV-screening visits, could be a clinically effective and cost-effective strategy in many settings. In addition, the HPV-FASTER proposal will merit further consideration when efficacy data on two vaccine doses for middle-aged women are made available, and when more information is available on the population-based effectiveness of the 9vHPV vaccine and the long-term follow up of cohorts with regard to the potential effect of cross-HPV-type protection of the 2vHPV vaccine[75,77].

Ongoing studies and trials

The HPV-FASTER concept has attracted significant attention and, to date, has resulted in the following related studies. In 2014, the European Commission funded a feasibility project in Europe to evaluate the acceptance of and compliance with a three-dose HPV vaccination regimen among women in the 25–45-year age group as well as the logistics of combining screening and vaccination infrastructures (CoheaHr)[134]. A previously created and successful collaborative consortium exploring alternative strategies in cervical cancer prevention in the European context is leading this research project, which is being conducted in 11 countries: Belgium,

Denmark, Finland, France, Germany, Italy, the Netherlands, Slovenia, Spain, Sweden, and the UK. This study will address some of the social and logistic uncertainties regarding the HPV-FASTER proposal. If the feasibility evaluation is successful, the consortium aims at organizing a full-scale controlled trial in which women aged 25–45 years will be randomly assigned to either an HPV-screening arm or an HPV-screening plus HPV-vaccination arm, with a 3–5 years follow-up duration. End points of the trial will include the incidence rates of HPV infections and cervical preneoplastic lesions.

The FRIDA trial[135,136], evaluating technologies for triage of HPV-DNA-positive women aged 25–75 years, is underway in two semi-rural areas in Mexico: Tlaxcala and Morelos. The trial is offering HPV testing and HPV16/18 typing to a large number of women who have previously had limited or no screening opportunities. In accordance with the HPV-FASTER protocol, the related FRIDA-2 trial intends to cluster randomize part of this screened population to either repeated HPV screening at 2 years and 5 years (control arm) or to receive HPV vaccination and repeated HPV screening at 2 and 5 years (intervention arm). The trial is powered to examine the gain in protection afforded by HPV vaccination in the 25–55-year age group (predicted long-term effects) over and above the short-term protective effects already established for one episode of HPV screening[135].

Other researchers are exploring opportunities of implementation of the HPV-FASTER concept in Latin America and in isolated populations, such the aboriginal migrant/refugee populations in Australia, in which repeated screening examinations are problematic. In addition, dissemination efforts are being made to organize HPV-FASTER research projects in other settings in both developed and developing countries. A panel discussion will be held in September 2015 at the International Papillomavirus meeting[137] to formally evolve towards the creation of an international HPV-FASTER consortium.

Conclusions

Two important tools are now available for improving cervical cancer prevention: one enhances secondary prevention by testing for the presence of HPV in cervical specimens and treating the HPV-induced lesions; the other introduces primary prevention by immunizing against a selected group of oncogenic HPV types. Adequately combined, these two options have the potential to dramatically control HPV-related cancers. Even after recognizing that some knowledge gaps require additional research, the time is now right to begin to evaluate strategies that would combine HPV-vaccination and HPV-screening strategies in the best possible way; we have proposed the HPV-FASTER concept as an example of how these complementary approaches could be combined. Cost–benefit analyses should advise the relevant public health institutions and the governments on the most cost-effective alternatives as well as on the range of prices at which cervical cancer control using HPV technologies would be sustainable.

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Author contributions

F.X.B., C.R., M.D., M.A., I.B. and J.C. researched the data for article and wrote the manuscript. All authors made substantial contributions to discussion of content and reviewed/edited the manuscript before submission.

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