Prevention of cervical cancer in developing countries

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Despite being a largely preventable disease, cervical cancer remains the most common cancer in women in developing countries, where screening is either limited or nonexistent. The health profile of women living in developing countries is dominated by the high prevalence of communicable and infectious diseases (TB, HIV and malaria) and maternal mortality. Diseases such as cancer of the cervix are barely recognized as a significant public-health problem. Another important barrier to establishing screening programs in poor countries is the requirements of cytology-based programs. Alternative protocols to cytology-based screening programs are explored in this paper, such as visual inspection and human papillomavirus (HPV) DNA testing. The advent of HPV vaccines has brought the issue of primary prevention of cervical cancer by vaccinating against the two most common types, HPV 16 and 18, into the spotlight, presenting a whole new range of challenges and opportunities.

Inequality and inequity of access to education, development and healthcare are recognized by the United Nations Millennium Development Goals as important determinants of poverty and human suffering [101]. The high prevalence of cervical cancer in poor countries is a stark reminder of the consequences of inequity of access to healthcare. Although there have been no randomized, controlled trials to evaluate the impact of cytology-based cervical cancer screening programs, data from case-controlled and cohort studies have shown a marked reduction in the incidence of, and mortality from, cervical cancer in those countries that have implemented mass screening programs, either organized, as in Finland or the UK, or unorganized, as in the USA [1–3]. However, there have been no successful screening programs in the countries of sub-Saharan Africa, Latin America, the Caribbean and south and south-east Asia. As a consequence, 80% of the approximately 500,000 new cases of cervical cancer diagnosed per year occur in these countries, which have access to less than 5% of the world's global cancer care resources [4].

The age-standardized incidence rates of cervical cancer range from less than 10/100,000 women in countries with national screening programs to over 50/100,000 in countries without screening programs; more than a fivefold difference [5]. Cytology-based screening programs require a relatively sophisticated healthcare infrastructure, including adequately equipped and staffed laboratories, functional referral systems, ongoing training and stringent quality control. In addition, cytological screening is coupled to colposcopy and histological sampling for women with an abnormal cervical smear; both require a level of clinical expertise usually only found in tertiary institutions or urban healthcare facilities in developing countries, if at all. The programs require substantial human, financial and other resources if they are to be successful. Initiating or sustaining such programs is prohibitively expensive for most poor countries, where the per-capita expenditure on health per year is often less than US$10, compared with approximately US$5000 in countries such as the USA [102].

Barriers to cervical cancer screening in developing countries

The health profile of women living in developing countries is dominated by the high prevalence of communicable diseases (e.g., TB and HIV), infectious diseases (e.g., malaria) and maternal morbidity and mortality. Healthcare services, which in general are poorly developed and underresourced in poor countries, tend to focus on these diseases, with cancer of the cervix barely recognized as a significant health problem. Competing health needs, widespread poverty, poor-quality health infrastructure, uninformed and disempowered women and endemic civil and environmental instability, among other factors, make the establishment of prevention programs in poor countries particularly challenging.

Primary & secondary cervical cancer prevention

The unique natural history of cervical cancer offers two key opportunities for prevention.

Keywords: cervical cancer, cytology, HPV DNA testing, human papillomavirus, screening, vaccination, visual inspection

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There is now convincing evidence that persistent infection of the cervix with oncogenic types of human papillomavirus (HPV) is necessary for the development of cervical cancer [6]. Persistent infection with HPV eventually leads to the development of intraepithelial neoplasia or lesions, progressing from low- to high-grade squamous intraepithelial lesions (SIL) or cervical intraepithelial neoplasia (CIN) and, ultimately, to invasive cancer [7]. Cervical cytology detects intraepithelial lesions, which, once detected and treated (usually by excision or ablation of the transformation zone), prevents the development of cervical cancer. This approach is known as secondary prevention as it interrupts the disease process once it has already been initiated.

Recently, two commercial companies have developed two different prophylactic vaccines that are able to prevent *de novo* infection with HPV, allowing for primary prevention (i.e., prior to the initiation of the disease process, which begins with HPV infection of the cervix) of cervical cancer. Preventing infection with HPV is expected to be a powerful new tool in the prevention of cervical cancer caused by the oncogenic HPV types 16 and 18. HPV vaccination will be discussed later in this paper.

Alternative screening methods: visual inspection with acetic acid

The challenges posed by cytology-based screening programs have prompted the search for alternative, technologically more appropriate and more affordable screening methods. Visual inspection with acetic acid (VIA) involves examination of the cervix after the application of 3–5% acetic acid, using the naked eye aided by a bright light source. VIA can be performed by mid-level health practitioners such as nurses, at a primary-care level and provides the patient with an immediate result, without the necessity of expensive laboratories and the infrastructure required by cytology. The test characteristics of VIA have been evaluated in a number of cross-sectional studies in developing countries, summarized by Sankaranarayanan *et al.* [8] and Denny [9]. These studies have included nearly 150,000 women and have reported sensitivities of VIA for high-grade intraepithelial lesions that have ranged from 49–96%, with specificities between 49 and 98%.

Recently, Sanakaranarayanan *et al.* have reported on a cluster-randomized trial performed in 114 clusters in the Dindigul district of India [11]. A total of 57 clusters or areas were randomized to one round of VIA by trained nurses, with colposcopy and histological sampling performed prior to treatment with cryotherapy if positive, and 57 to a control group. This study was the first to report on a reduction in cervical cancer incidence in the intervention versus the control group (all other VIA studies have used intraepithelial lesions as the outcome). In the intervention group, 274,430 person-years, 167 cervical cancer cases and 83 cervical cancer deaths were accrued (crude rate: 30.2/100,000 women person-years) compared with 178,781 person-years, 158 cases and 92 deaths in the control group (crude rate: 51.5/100,000 women person-years) between 2000 and 2006.

Denny *et al.* performed a randomized, controlled trial of 6555 women aged 35–65 years in Cape Town, South Africa [12]. This trial evaluated three 'screen and treat' strategies:

- Screening with VIA followed by cryotherapy if positive;
- Screening with HPV DNA testing using Hybrid Capture® II (Digene Diagnostics, MD, USA) followed by cryotherapy if positive;
- The control group had delayed treatment for 6 months regardless of the result of the screening tests (VIA and HPV DNA testing).

The prevalence of high-grade cervical cancer precursors (defined histologically) was significantly lower in the two screen and treat groups 12 months post-randomization compared with the delayed-evaluation group. HPV DNA testing followed by cryotherapy was twice as effective in reducing high-grade lesions compared with VIA followed by cryotherapy. The cumulative detection of CIN 2+ in women in the 'HPV DNA and treat' group was 1.42%, 2.91% in the 'VIA and treat' group and 5.41% in the delayed-treatment group. While minor complaints, such as discharge and bleeding, were common after cryotherapy, major complications were rare. While the study was not designed to evaluate the HIV transmission rate in treated versus untreated women, there was no increase in HIV transmission in these two groups.

VIA lends itself to screen and treat strategies and has many advantages in low-resource settings, particularly the option of a 'one-stop' visit to the clinic. Disadvantages of VIA include its relatively low specificity and positive predictive value (PPV), resulting in considerable over-treatment. In addition, it is very difficult to provide reliable quality control of VIA, which may lead

to very different performance characteristics in different settings. However, despite its shortcomings, no other current screening option is economically viable in many poor countries. Currently, the WHO is funding VIA and treat roll-out studies in six African countries and preliminary reports are very positive, indicating that 'something is better than nothing' [10]. VIA has enabled severely resource-restricted countries to establish some form of screening infrastructure for older women. While the impact on cervical cancer prevention is likely to be modest to small, creating an infrastructure for the healthcare of older women is a very good start. The study in India [11] clearly indicated that a VIA and treat program was associated with a significant reduction in cervical cancer compared with no screening at all.

Visual inspection with Lugol's iodine (VILI; originally known as Schiller's test, a test introduced by Schiller in the 1930s that was rapidly replaced by cytology when it became available [13]) involves washing the cervix with Lugol's iodine to identify mustard-yellow areas on the cervix, which would correspond to cells low in glycogen, including metaplastic cells, columnar epithelium and dysplastic epithelium. A multicentered study in India and Africa involving nearly 50,000 women concurrently evaluated VIA and VILI by independent providers [14]. The pooled sensitivity and specificity to detect high-grade intraepithelial lesions (CIN 2/3) were 92 and 85% respectively, compared with 77 and 86% for VIA. However, in a study in Peru, VILI had a significantly lower sensitivity of 53% and a specificity of 78% to detect CIN 2/3 [15]. In a study in the Congo of 1528 women, VILI (when performed by nurses) had a sensitivity of only 44% and a specificity of 97% [16]. These variable findings are important to note, and may well reflect the difficulties inherent in all subjective tests, whether visual inspection or discerning the morphology of individual cells.

Goldie *et al.* investigated the cost–effectiveness of a variety of cervical cancer screening strategies in India, Kenya, Peru, South Africa and Thailand [17]. They reported that screening women once in their lifetime, at the age of 35 years, with a one- or two-visit strategy using VIA reduced the lifetime risk of cervical cancer by approximately 25–36% and cost less than 500 international dollars per year of life saved. Relative cancer risk declined by an additional 40% with two screenings at ages 35 and 40 years. The study concluded that VIA (followed by immediate treatment of positive cases, on site) or two clinical visits (followed by treatment without prior colposcopic evaluation of positive cases) is one of the most cost-effective alternatives to conventional three-visit screening strategies using cytology, followed by colposcopy and biopsy of positive cases and then treatment of high-grade precursors.

Human papillomavirus DNA testing

Infection of the cervix with oncogenic types of HPV is necessary for the development of cervical cancer, and oncogenic HPV is detectable in nearly all cervical cancers [18]. In the 1990s, an assumption was made that detecting the causative agent of cervical cancer would have acceptable diagnostic performance, and being an objective test, would overcome the subjective nature of cytology. HPV DNA testing has been studied in a variety of clinical settings:

- Triage of borderline or minor cytological abnormalities;
- Primary screening test;
- In combination with other screening tests, for example, cytology or VIA.
- For follow-up post-treatment for cervical cancer precursors.

It is beyond the scope of this article to review the extensive literature on HPV DNA testing and screening. There is a number of comprehensive reviews to which the reader is referred [19–22]. To summarize, HPV DNA testing, whether by Hybrid Capture, which is US FDA-approved, or PCR-based assays (no commercial or FDA-approved kits available to date), in both cross-sectional and longitudinal studies, has been shown to:

- Consistently and in different settings have higher sensitivity than cytology for the detection of high-grade precursors (in most studies HPV testing is 20% more sensitive than cytology [19,21]);
- Consistently and in different clinical settings have a lower specificity and PPV compared with cytology, with a false-positive rate of approximately 5% [21];
- Have a negative predictive value of virtually 100%, with women negative for high-risk HPV being at very low risk for cervical cancer;
- Have a significantly higher sensitivity than cytology for detection of persistence/recurrence of SIL/CIN post-treatment;
- Be more reliable, reproducible and objective than cytology.

HPV DNA testing has been recommended as a primary screening test in women over 30 years of age, followed by cytology for women with a positive test [23]. In this study, Cuzick *et al.* followed 10,358 women with a mean age of 42 years who presented for routine screening in the UK in the HPV in Addition to Routine Testing (HART) study. This study showed that HPV testing was more sensitive than borderline or atypical cells of undetermined significance or worse cytology, with HPV DNA testing having a sensitivity of 97% compared with 77% for cytology for the detection of high-grade SIL. Of note, no woman who had a negative initial HPV test or an atypical cells of undetermined significance cervical smear had a high-grade SIL lesion after 12 months of follow-up. This approach could potentially improve detection rates of high-grade SIL without increasing the colposcopy referral rate, as HPV-positive women, with negative cytology, would be managed by repeat testing after 12 months instead of being referred for colposcopy.

The low specificity of HPV DNA testing is of concern, particularly in large-scale screen and treat programs, as a high false-positive rate would lead to significant overtreatment of women. However, women who have a positive test for high-risk HPV are at considerable risk of developing SIL or CIN in the future, and warrant more intensive surveillance. Castle *et al.* followed over 2000 women who had negative cytology but a positive high-risk Hybrid Capture® II HPV DNA test for a 57-month period, and found that 15% of these women developed an abnormal Pap smear in this nearly 5-year period [24]. Similarly, Koutsky *et al.* showed that 28% of women who were high-risk HPV-positive with negative cytology developed high-grade SIL over a 25-month period, compared with 3% of HPV-negative women [25]. Rozendal *et al.* reported that women with negative cytology but a positive HPV test had a 116-fold increased risk of developing CIN 3 compared with HPV-negative women over a 40-month follow-up period [26].

Another way in which HPV DNA testing could be utilized as a primary screening test is to screen women using self-collected vaginal samples. Wright *et al.* reported on supervised self-testing for high-risk types of HPV DNA in a South African study [27]. The sensitivity of HPV DNA testing of a self-collected vaginal sample for high-grade SIL or cancer was 66% (95% CI: 52–78%), which was equivalent to that of conventional cytology. By contrast, the sensitivity of HPV DNA testing of a clinician-obtained sample was 84% (95% CI: 71–92%), which was significantly higher than that of cytology or a self-collected sample.

Oglivie *et al.* performed a meta-analysis of 12 studies on the diagnostic accuracy of self-collected vaginal samples compared with clinician-collected vaginal samples [28]. In six studies in which Dacron or cotton swabs or cytobrushes were used, the overall sensitivity was 74%, with a specificity of 88% of self-collected samples for high-grade precursors. Although inferior to clinician-obtained samples, self-sampling has sensitivity higher than cytology, and may be a useful way of including women in screening programs who are reluctant to undergo gynecological examinations.

HPV DNA testing offers some advantages over cytology, but is currently far too expensive for developing countries, and the laboratory infrastructure is too sophisticated. In addition, HPV DNA testing, while more efficient and able to process many more samples per day compared with cytology, is still a laboratory-based test with all the disadvantages this holds for countries with a resource-restricted healthcare infrastructure. However, there has been an initiative by PATH, an American-based non-governmental organization with funding from the Gates Foundation, in collaboration with two commercial companies, to develop two rapid biochemical tests for HPV DNA testing [103]. The test, developed in collaboration with Digene, uses hybrid capture technology and detects the most common oncogenic types of HPV, and is able to process dozens of samples in approximately 2.5 h. In the second test, developed in collaboration with Arbor Vita (CA, USA), research is taking place into the feasibility of a rapid strip test that will process a sample within 15 min. This test detects the presence of a protein induced by HPV-infected cells, indicating loss of control over cell reproduction. Field testing of both tests is being performed in India and China. The costs of the tests have not been revealed, but the intention is to make them affordable in the developing-country context. Rapid testing, if validated, will allow screen and treat protocols to be implemented in poor countries and, as shown by Denny *et al.* [12], is likely to be twice as effective as VIA and treat in preventing cervical cancer.

Another important consideration with regards to HPV DNA testing is the prevalence of infection of HIV, which is very high in many developing countries. Of the approximately 40 million HIV-infected individuals in the world at the end

of 2006, 25 million were resident in sub-Saharan Africa, and over 50% of those infected were women [104]. The expected increase in women diagnosed with cervical cancer in Africa during the HIV pandemic has not been convincingly observed, most likely owing to most at-risk women dying from other opportunistic infections prior to developing cervical cancer or its precursors. However, in the era of antiretroviral medication, this scenario may change. Studies have consistently shown higher prevalence of HPV infection, persistent infection with HPV, infection with multiple types of HPV and higher prevalence of cervical cancer precursors in HIV-infected women [29–31]. The high prevalence of HPV-associated disease in these patients will most likely render HPV DNA testing far too nonspecific for it to have a meaningful role in screening. In fact, to be provocative, owing to the very high prevalence of HPV infection in HIV-infected women, there have been suggestions that all HIV-positive women undergo prophylactic ablation of the transformation zone of the cervix without prior screening. However, this is an untested approach.

Primary prevention of cervical cancer through vaccination

The development of two vaccines against HPV is a dramatic new development in the armamentarium of tools for the prevention of cervical cancer. Monovalent, bivalent and quadrivalent vaccines have been tested in randomized, controlled trials and have shown remarkably consistent results in providing protection against the types included in the vaccines. The vaccines tested in clinical trials use HPV type-specific L1 proteins that self assemble into noninfectious, recombinant virus-like particles. The bivalent vaccine, against types 16/18 (Cervarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium), is administered at months 0, 1 and 6 by intramuscular injection. The quadrivalent vaccine (Gardasil®, Merck and Co., Inc, NJ, USA) is administered at months 0, 2 and 6, also via intramuscular injection.

Studies from a number of randomized trials have shown all three vaccine formulations to be safe, immunogenetic and efficacious at preventing infection with the types included in the vaccines for up to 6.5 years [32–37]. As the vaccines are prophylactic, they should ideally be administered to individuals prior to the onset of sexual activity, which varies considerably from country to country and in different cultures. Vaccination of children (e.g., ages 9–12 years) is most likely the most clinically effective and cost effective strategy [39]. Vaccination of adolescents and young adult women (so-called 'catch-up vaccination') is also important, but it will be less cost-effective and less effective with increasing age, as an increasing proportion of women will have been exposed to HPV. Once already infected with the type of HPV in the vaccine, vaccination will not have any effect. The vaccine is purely prophylactic, not therapeutic.

In a study of the cost–effectiveness of vaccinating against types 16 and 18, Goldie *et al.* showed that vaccination alone, assuming 70% coverage of girls aged 9–12 years, is expected to reduce the lifetime risk of cervical cancer by approximately 43% [40]. However, a combined approach of vaccination of young girls and screening women over the age of 30 years, at 70% coverage for both, will provide additional benefits with an estimated 53–70% reduction in the lifetime risk of cervical cancer. At coverage rates of 100%, the expected cancer reduction with vaccination alone would be 61%, and with the combination of vaccination and screening older women, cervix cancer reduction reaches 75%. The two most important factors influencing the predicted impact of HPV vaccination include achieving high coverage of the targeted population, and the ability to achieve high efficacy by vaccinating girls prior to the onset of sexual activity and, therefore, acquisition of HPV infection.

From a developing-country perspective, the implementation of the HPV vaccine poses many considerable challenges, which will take years to overcome. The first is the cost, which, at current prices, is unaffordable for almost all developing countries. Historically, new vaccines have only been made available to people in the developing world many decades after being available in industrialized countries. The hepatitis B vaccine was licensed in 1981, but only became available to the world's poorest developing countries 20 years later [41]. Furthermore, it was only once the price of the hepatitis B vaccine had fallen below the 25 cents (USA) level and the vaccine was incorporated as an infant vaccine that coverage in developing countries reached acceptable levels. This was aided by the GAVI Alliance, which is credited with enabling 158 million children to be immunized against hepatitis B between 2000 and 2006 [105]. Both HPV vaccines are the most expensive vaccines ever to be developed and, despite commitments from the commercial companies to introduce tiered pricing for low-income countries and the

possibility of subsidization from organizations such as the GAVI Alliance, cost is likely to be prohibitive for some time to come, or at least until the companies have recouped their costs and made their projected profits.

However, purchasing the vaccine is one small cog in a much more complex machinery. At the most basic level there are technical issues of the vaccines, which include requiring a cold chain (they need to be stored at between 2 and 8°C), the necessity for three intramuscular injections (clinical skills, follow-up strategies and disposal systems required), adequate storage facilities, reliable supplies of power (electricity or other source – notoriously unreliable in developing countries) and trained personnel. More challenging than these factors, however, is how to create the platform for recruitment of the targeted population of children, ideally girls aged 9–12 years of age, along with the appropriate infrastructure to administer three vaccines at months 0, 1 or 2 and 6.

In terms of recruitment, there are a number of barriers from the developing-country perspective, which include:

- No adolescent/prepuberty health infrastructure for vaccine administration in any developing countries – all vaccine schedules are targeted to infants and young children through National Immunization Programs and Extended Programs for Immunization;
- Limited availability of school health systems in developing countries, where, ideally, access to young girls would be best;
- Many girls in developing countries do not complete primary school, so even where school health systems do exist, girls may miss out on vaccination (however, achieving universal primary education for girls and boys is one of the eight Millenium Development goals and progress in being made in this arena [101]);
- Even in highly educated communities with access to all modern facilities for acquiring information, knowledge regarding HPV and its connection to cervical cancer is very poor, even more so in developing countries. Furthermore, the sexual nature of HPV transmission raises many taboos and may prevent mothers from allowing their daughters to be vaccinated. In Africa, this problem is further compounded by many people confusing the abbreviation of HPV with HIV, increasing the stigmatization. Providing accessible, culturally appropriate and informative resources to poorly educated individuals has its own challenges, and will require considerable financial and creative input to be effective;
- Provider knowledge regarding HPV is also limited [42], making education of healthcare professionals an important part of vaccine implementation strategy;
- Data on the efficacy of the vaccines in HIV-positive individuals is not yet available, and this information is critical for vaccine implementation in areas at the epicenter of the HIV epidemic in many developing countries;
- Furthermore, data on the long-term duration of protection and the necessity for booster doses are still awaited, although all the evidence to date suggests that, at least in immune-competent individuals, the vaccines induce immune memory, an important characteristic of vaccines that provide long-lasting protection [43].

Despite the many challenges discussed above, the HPV vaccines also provide new opportunities for developing countries. Prepubescent and adolescent health, like that of older women, has traditionally been neglected in developing countries. Creating a health platform for this age group could provide an opportunity for many potentially useful health interventions, for instance, to provide young people with information on: sexuality, safe sex practices, sexually transmitted infections and their short and long-term consequences, prevention of HIV, pregnancy prevention and contraception, the dangers of drug and alcohol use and abuse, and many others. From a health point of view, besides vaccinating against HPV, it may also provide an opportunity for booster doses, for example, against hepatitis B, tetanus and, potentially, HIV, if such a vaccine were to be developed. Other health interventions include deworming programs and assessment of nutritional status, among others.

Ultimately, the decision to introduce a vaccine into a healthcare system is a political decision usually strongly influenced by economic realities. Issues such as the burden of disease and local epidemiology, cost and affordability of the vaccine, competing priorities and so on will all influence the decision to incorporate a new vaccine. Currently, most governments have advisory boards determining which vaccines will receive priority implementation. As immunization is focused on infants and young children, most of these advisory boards are staffed with individuals involved with child health. This community has

Executive summary

- Cytology-based programs for secondary prevention of cervical cancer that have achieved wide coverage of the targeted population and provided treatment of abnormalities detected have dramatically reduced the incidence of and mortality from cervical cancer. As a consequence, cervical cancer has become a rare disease in these countries. However, in much of the developing world, establishing cytology-based screening programs has proven to be prohibitively complex. Thus, very little cervical cancer screening occurs in the developing world, accounting for cervical cancer remaining the most common cancer among women in these countries.
- In the past decade and a half, researchers in a number of developing countries have been investigating alternative protocols for the prevention of cervical cancer in low-resource settings. Two of the most investigated alternatives are visual inspection with acetic acid (VIA) and human papillomavirus (HPV) DNA testing.

Summary of the studies of over 150,000 women using VIA in various study designs has shown the following:

- Sensitivity equivalent to or greater than cytology for detection of high-grade cervical cancer precursors.
- Specificity and positive predictive value are both lower than cytology, and will result in overtreatment of women included in 'screen and treat' protocols.
- VIA gives an immediate result, uses low technology and is affordable as a consequence.
- VIA allows for women to be included in screen and treat protocols without the pretreatment use of colposcopy or histological sampling, obviating the need for a laboratory infrastructure.
- While overtreatment is acknowledged, complications from treatment appear to be minor, and overall treatment is considered to be safe and acceptable to women if cryotherapy is used.
- One randomized, controlled trial in India has shown a reduction in cervical cancer of approximately 25% in women screened with one round of VIA and treated with cryotherapy if positive, compared with unscreened women.
- The main disadvantage of VIA is the variable performance in different settings, requiring stringent quality-control methods, which are difficult to implement at large scale.

HPV DNA testing has been consistently shown to have:

- Significantly higher sensitivity than cytology for the detection of high-grade precursors, despite lower specificity and positive predictive value, but nearly 100% negative predictive value.
- Women who are negative for high-risk types of HPV have minimal risk of developing cervical cancer precursors and can receive a high level of reassurance.
- Women who have a positive high-risk HPV test but negative cytology are at considerable risk of developing cervical cancer precursors over time.
- Current methods for HPV DNA testing are unaffordable in developing countries, but initiatives are afoot to develop rapid tests that will give a real-time result and be affordable for developing countries. The outcomes of validation studies of these new tests are awaited.

Vaccination against HPV

While primary prevention of cervical cancer by vaccination against the commonest types of HPV associated with cervical cancer is one of the most promising breakthroughs in modern medicine, implementing the vaccine in developing countries poses many challenges. These range from:

- Cost and affordability.
- Establishing the programmatic components of a prepubescent/adolescent vaccine platform, from recruitment to follow-up over a 6-month period, in countries where, traditionally, vaccination is aimed at infants and young children.
- Educating parents, children, politicians, health-policy decision makers and healthcare professionals will take considerable effort, resources and creativity.
- Technical difficulties include the necessity of maintaining a cold chain, creating the infrastructure to administer three intramuscular injections over a 6-month period and providing adequate transport and storage facilities.
- The impact of HPV vaccination will be considerably delayed, particularly in developing countries, which may result in failure to persuade politicians of its benefits.

very little to do with the women's health/cancer community, and thus awareness of the prevalence, morbidity and mortality associated with cervical cancer is low. For effective implementation of the vaccine against HPV, these two different communities will need to establish meaningful contact.

In addition, data on the incidence of cervical cancer (through population-based registeries) and of HPV-associated disease of the genital tract is limited in developing countries, particularly sub-Saharan Africa, and the true incidence and prevalence is most likely underestimated. This information is important to accrue in order

to give a true indication of where cervical cancer fits into the spectrum of disease in any given country. Other issues not specifically addressed in this section include the possibility of vaccinating males to increase herd immunity (defined as the positive benefits of vaccination to the nonvaccinated persons in the population through reduced HPV prevalence), which, according to the model used by Goldie *et al.* [40], would have a modest impact on cancer reduction if vaccine coverage among girls was relatively low (between 50–70%), but a very low impact if coverage of girls were to reach 90%.

Conclusion

Cervical cancer remains the most common cancer diagnosed in women living in poor countries, largely owing to the failure to initiate or sustain secondary prevention programs for the prevention of cervical cancer. While imperfect, alternative protocols to cytology-based screening programs, such as VIA and HPV DNA testing, have shown equivalent or substantially better sensitivity for the detection of high-grade cervical cancer precursors, although consistently lower specificity and PPVs. Nevertheless, one well-designed, randomized trial has shown reduction of cervical cancer, using VIA, colposcopy and treatment, and another, using a screen and treat protocol without prior colposcopy and histological sampling, has shown a reduction in cervical cancer precursors.

Vaccination against HPV is expected to have a major impact on cervical cancer prevention; however, the true impact in developing countries will be considerably delayed owing to the many logistical, economic and programmatic issues that need to be overcome. Many developing countries do not have the most basic screening programs, or even awareness of the importance of cervical cancer as an often lethal and common disease among poor women. Advocates for women's health and the cancer community have a great deal of work to do if the HPV vaccine is to be distributed to developing countries, bearing in mind the consequences, ethics and injustice of the 'inequity of distribution of healthcare resources' experienced globally.

Future perspective

In 10–15 years time, it is hoped that both vaccines will show long duration of protection with the induction of immune memory, and obviating the need for booster doses to maintain immunogenicity and efficacy of the vaccines against HPV types 16 and 18. It will most likely take this amount of time for the vaccines to be meaningfully introduced into developing countries, owing to the considerable complexity of introducing the vaccines to a new platform of individuals. It will take at least another 20 years for the real impact on cervical cancer to be appreciated.

Financial & competing interests disclosure

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