Ensuring access to HPV vaccines through integrated services: a reproductive health perspective

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Abstract In 2006, a quadrivalent human papillomavirus (HPV) vaccine was licensed, and another vaccine may be licensed soon. Little is known about the practical considerations involved in designing and implementing cervical cancer prevention programmes that include vaccination as a primary means of prevention. Although the vaccine may ultimately be indicated for both males and females, young girls, or girls and women aged 9–25 years, will be the initial candidates for the vaccine. This paper describes avenues for service delivery of HPV vaccines and critical information gaps that must be bridged in order to inform future sexual and reproductive health programming. It proposes the role that the sexual and reproductive health community, together with immunization and cancer control programmes, could have in supporting the introduction of HPV vaccines within the context of current health systems.

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Introduction

Cervical cancer is a gender-specific disease that disproportionately affects women in the lowest socioeconomic classes throughout the world. A meta-analysis of 57 studies revealed that there was an estimated 100% increased risk of invasive cervical cancer for women in low social class categories when compared with those in high social class categories; this difference reflects a lack of access to screening and treatment services.[1] Likewise, these differences also occur between developed and developing countries, translating inequity in access to inequity in the quality services.

In 2004, the 57th World Health Assembly adopted WHO's global reproductive health strategy, which identified five priority areas including "combating sexually transmitted infections"; the strategy also specifically addressed cervical cancer prevention.[2] In addition, a resolution on cancer prevention and control was adopted by WHO's Member States, and a new vision and strategy for global immunization that aims to ensure equal access to immunization for every child, adolescent and adult was endorsed during the 58th World Health Assembly in 2005. With the upcoming introduction of a vaccine to prevent human papillomavirus (HPV) infection, a comprehensive approach to preventing cervical cancer — which incorporates vaccination, screening and early treatment — opens up new opportunities for strengthening reproductive health services and building interdisciplinary links.

Cervical cancer: burden of disease

Cervical cancer remains the second most common cancer in women worldwide and the primary cause of cancer-related deaths among women in developing countries.[3] Screening programmes have successfully reduced disease rates in developed countries that support cytology-based services; these services are too complex for most developing countries to implement. More than 80% of the estimated 500 000 incident cases annually and more than 90% of the 257 000 deaths caused by cervical cancer occur in developing countries (Fig. 1).[4] This disparity is due in large part to the fact that a majority of women in these countries have never been screened for cervical cancer.

HPV infection

HPV is a sexually transmitted infection, recognized as the necessary cause of 99% of all cervical cancers. More than 100 types of HPV have been identified, including at least 13 types that may cause cervical cancer: these are termed "high-risk" types. Of these, HPV types 16 and 18 cause approximately 70% of cervical cancer worldwide.[5] There is geographical and country-specific variability; in sub-Saharan Africa and Latin America types 16 and 18 account for only 65% of invasive cancers. Other, "low-risk" types, mainly 6 and 11, cause genital warts in men and women but not cervical cancer.

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In most studies, the age-specific peak prevalence of HPV infection occurs among those aged < 25 years, and the peak incidence of cervical cancer occurs at around age 50.[5,6] Although 90% of all HPV infections are cleared, persistent infection in some women leads to the development of cancer 20 or 30 years later. This prolonged latent phase allows for screening of the cervix to detect precancerous abnormalities.

Cervical cancer screening: secondary prevention

Cervical cancer prevention programmes have been cytology-based, but their success depends upon having high rates of coverage of women in the right age group, implementing repeated quality-controlled screening and developing excellent recall services for treating precancerous abnormalities. In low-resource settings, the capacity to implement this complex, high-resource protocol to cover entire populations has been limited.

Alternative cost-effective screening and management options include visual inspection with acetic acid (VIA), with immediate cryotherapy of visible cervical lesions, and testing for HPV DNA;[7,8] these options also improve efficiency by limiting the steps a woman needs to take to access treatment.[9] When compared with cervical smear methods, the DNA screening test appears to be cost-effective, is more objective and less labour-intensive, and has high sensitivity and specificity.[10] Although the current DNA test is too expensive for use in developing countries, lower-cost tests are being developed.

HPV vaccines

HPV vaccines are prepared from virus-like particles produced by recombinant technology. The quadrivalent vaccine (Gardasil, Merck and Co., Whitehouse Station, NJ, USA) has recently been licensed, and a bivalent vaccine (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) is in advanced stages of clinical testing. These HPV vaccines are designed to prevent infection with and disease from HPV 16 and 18; the quadrivalent vaccine also protects against low-risk genotypes 6 and 11. The vaccines are not designed to treat people who have already been infected with these genotypes. The results from phase III trials of Gardasil, show that it provides almost 100% protection against moderate and severe cervical intraepithelial neoplasia (CIN 2 and CIN 3) caused by the genotypes in the vaccine among women who have not previously been infected with these genotypes.[11] Gardasil has also been shown to protect against external genital lesions caused by types 6 and 11, which Merck hopes will make the vaccine more attractive to men as well as women.[11,12] Trial data for both vaccines suggest they offer a minimum of 4–5 years' efficacy, of close to 100%, in preventing persistent infection by the vaccine genotypes.[13,14] The actual impact of the vaccine will be highly dependent on country-specific parameters.[15]

Knowledge gaps

Although the results of vaccine trials are promising, gaps in the evidence that will inform service implementation remain.[16,17] These gaps are outlined below.

- **Performance in Africa.** Both vaccines lack safety and efficacy data from Africa where chronic malnutrition, HIV and other infectious diseases that may compromise the immune response are widespread.
- **Duration of action.** Data showing that antibodies persist at levels as high as, or higher than, those seen in natural infection extend to almost 5 years' post-vaccination; antibody levels plateau after 18 months.[13] As further data accrue from extended follow-up of clinical trials, the need for a booster dose can be evaluated.
- **Data on different immunization schedules.** Evaluation is required of the degree of flexibility in intervals between doses and the possibility of two doses being sufficient.
- **Data on infants and young children.** Lack of safety and immunogenicity studies in infants or young children will hinder the integration of vaccines into the traditional Expanded Programme on Immunization (EPI) schedule, which is tailored to childhood vaccination.
- **Cross-protection.** Data on Cervarix indicate there is a high level of cross-protection against new infections with HPV type 45 and a moderate level of protection against type 31,[13] which together are responsible for a further 10% of cervical cancers globally. For the quadrivalent vaccine, antibodies capable of neutralizing both vaccine-type and HPV types 31 and 45 have been demonstrated.[18] Studies on both vaccines continue to evaluate cross-protection against clinical disease associated with these types.
- **Potential replacement infection.** Increases in the prevalence of infection with other types of HPV that develop to fill the "ecological niche" of persistent infection — once infection by types included in the vaccines no longer have that role — will become apparent only during post-introduction surveillance.
- **Vaccine compatibility.** For the quadrivalent vaccine, immunogenicity data show no interference when hepatitis B vaccine is administered simultaneously.[11] Administration of HPV vaccine in combination with other vaccines has not been tested nor have the vaccines been tested in people who are on long-term drug therapy. Bridging studies should address these issues.

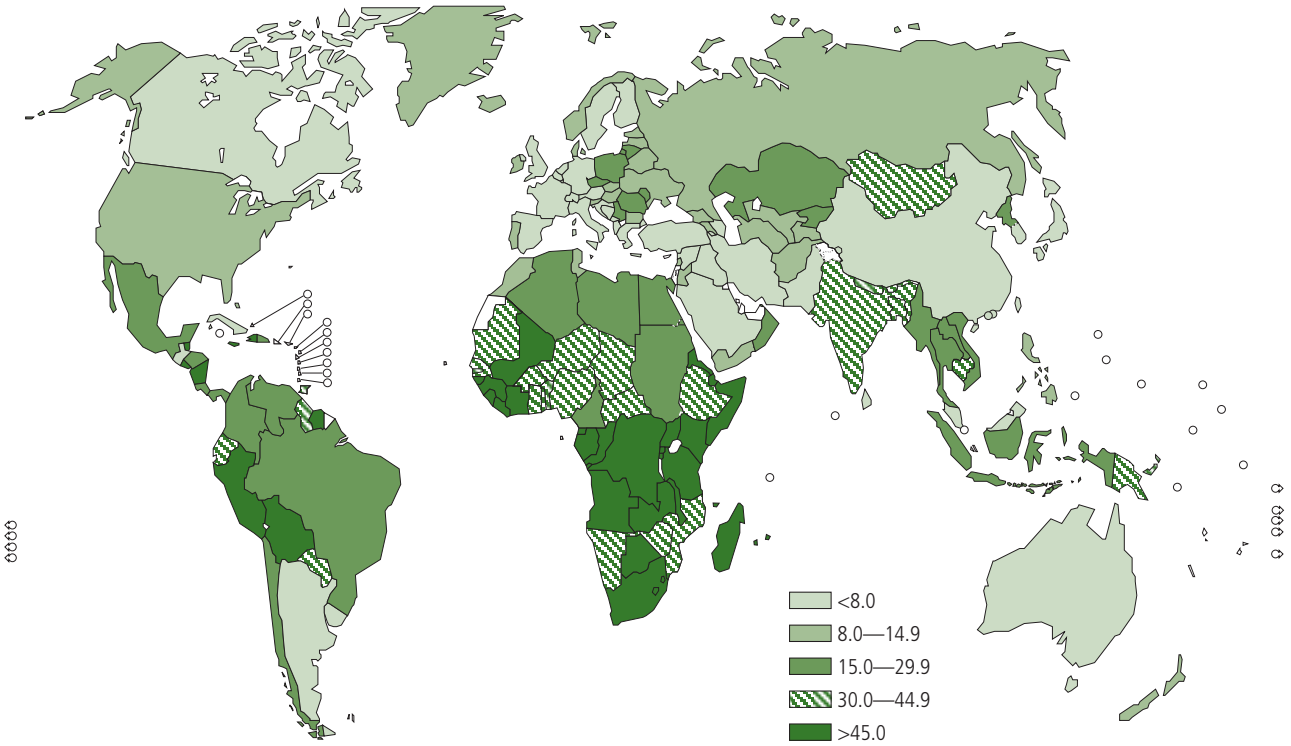
Critical programmatic issues for introducing HPV vaccines

Advocacy, information and education

International public health advocacy at the highest level was instrumental in obtaining a purchasing commitment from the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) for hepatitis B vaccine as well as a ranking scheme that assisted donors in their decision-making about financial support.[19] In the case of cervical cancer prevention, advocacy must come from those who understand the disease and its societal and population-based burden. Surveys have indicated that knowledge about HPV and cervical cancer among women, men and even health professionals is relatively low.[20] Health professionals at all levels and policy-makers have the greatest opportunity to generate political will and, therefore, need to be well informed.[21]

Since HPV is sexually transmitted, culturally appropriate information must be developed to avoid a negative reaction against vaccination or sexual and reproductive health services, particularly since young girls will be the ones who are vaccinated. It is also important to avoid the risk of a girl-only focus; even if only women and girls receive the vaccine, information must also be given to men and boys about cervical

Fig. 1. **Worldwide incidences of cervical cancer per 100 000 females (all ages), age-standardized to the WHO standard population, 2005**[4]



cancer and behavioural interventions to reduce HPV transmission. Targeted and adapted information will help to avoid discrimination or other kinds of misunderstanding. Several studies have demonstrated that if parents understand the benefits of vaccination their apprehension about discussing issues of sexual health or acknowledging that their child may be, or may become, sexually active can be overcome.[22]

Evidence-based standardized informational materials should be developed or identified for wide distribution by health professionals. The significant role of the sexual and reproductive health community in nurturing advocates to campaign for the adequate allocation of resources, nationally and internationally, must not be underestimated. Comprehensive prevention programmes that offer screening and early treatment alongside new vaccine programmes would allow an opportunity to provide community-based education regarding sexual and reproductive health in broader terms.[23]

Target populations

Adolescent girls

Data indicate that for greatest impact the vaccine will need to target girls before they initiate sexual activity (that is, before sexual debut), beginning, for example, at the age of 9 years, possibly with additional catch-up vaccination of young women up to the age of 25 years, where resources permit. Infection with high-risk HPV types is consistently high among almost all adolescent female populations tested. Although efficacy trials did not include girls aged < 15 years,[24] bridging studies have established that antibody responses in girls and boys aged 9–15 years are higher than in older people.[25,26]

Providing a vaccine "against cancer" to adolescent girls raises several challenges. For the vaccine to be acceptable, parents will need to have a better understanding of cervical cancer and the reasons for vaccinating young girls to prevent a disease from occurring decades later. A sobering lesson may be gleaned from past efforts to eradicate poliomyelitis that were complicated by misinformation or rumors.[27] Although European studies report high acceptability rates for HPV vaccine,[28,29] there is a clear lack of understanding of the causes of cervical cancer across class and national lines.

Many young unmarried girls and women face significant challenges in accessing the health care necessary to meet their sexual and reproductive health needs. While neither national immunization programmes nor sexual and reproductive health programmes are ideal for providing services to young adolescents, a package of health services should be developed to offer girls an HPV vaccine and other interventions that could have a broader impact on their reproductive health.

Boys and men

HPV prevalence is lower in men than in women, although it is still frequent; it is not known whether men clear such infections more quickly or are less likely to be infected.[30] Although one of the vaccines may be licensed for use in males, modelling studies suggest this will reduce cervical cancer only marginally when coverage in women is very high.[31] There are, however, other reasons to consider male vaccination.

Gardasil, and possibly later-generation vaccines, will provide protection against genital warts and other external genital lesions[11,32] that affect both women and men. HIV infection is associated with an increased prevalence of genital warts, and giant condyloma (Buschke–Löwenstein tumours) have also been observed in HIV-positive patients who have histological evidence of invasion without metastases.[33]

Both men and women who practice receptive anal sex are at risk of developing anal intraepithelial neoplasia, the precursor to anal cancer, which is also linked to HPV infection.[34] HIV-positive men with HPV are twice as likely to develop anal cancer as men who are HIV-negative.[30]

Studies suggest that education and information actively designed to inform men about cervical cancer have an impact on their female partners' willingness or ability to access services.[35] Ultimately, resources should be directed first towards the targeted age and sex of the population; however, the involvement of both males and females in vaccination efforts might increase acceptability, both directly and indirectly.

Potential delivery strategies

National immunization programmes

Despite the successes of EPI there are several programmatic challenges in introducing HPV vaccines as part of the programme in many countries.[16] It may seem attractive to link HPV vaccine to tetanus toxoid administration because both target young adult women, have a schedule requiring three or more doses, and have similar intervals between doses. However, coverage of tetanus toxoid through routine services reaches only around 50% globally, and much of the vaccine is given to parous women.[16] Tetanus toxoid is also given to school-aged children, but can be given at the time the child starts school since the duration of immunity is known. Given the limited data on the duration of protection of the HPV vaccines, and absence of clinical trials in children aged < 9 years old, school entry would be too early for co-administration.

School-based vaccination

Where enrolment rates are high, school-based vaccination may be extremely successful in eliminating disease.[36] Parents usually trust health-care recommendations made in a school setting, especially when they are endorsed by professionals involved in the setting, such as teachers.[37] In countries where education is mandatory and/or accessible to all children, laws mandating vaccination before enrolment may increase vaccination rates by as much as fourfold.[38] School-based vaccination may be cost-efficient because children are already gathered in one place and accounted for.[39]

However, in many countries, by the age of 9 years only a minority of girls are still in school.[40] Poor enrolment rates, limited school facilities in rural areas, migration and school fees are obstacles that prevent many girls from remaining in school until an age appropriate for HPV vaccination.[41] For countries with low school attendance among girls aged ⩾ 9 years, the most practical delivery method may be through annual immunization campaigns. However, delivering HPV vaccines through such campaigns would require evaluation of a schedule with a longer interval between the second and third doses than has been administered in trials.

Sexual and reproductive health services for adolescents

Sexual and reproductive health services, and family planning services in particular, are almost exclusively accessed by women during or following a first pregnancy and access is motivated by a desire to space births rather than to delay early childbearing.[42] Young women aged 9–25, and especially unmarried women in that age range, have particular difficulty overcoming social and political barriers to gaining access to reproductive health services.[43,44] The time between early childhood and sexual debut defines one of the most difficult cohorts to reach for health care.

Adolescent health programmes are developing user-friendly services that aim to provide counselling on sexual health that focuses on the prevention of pregnancy and sexually transmitted infections including HIV. The presence of a new intervention, such as an HPV vaccine, could extend the scope of these services and help to integrate other interventions, thereby making them more attractive to young people.

Role of sexual and reproductive health services

Existing sexual and reproductive health programmes can have an important strategic role in integrating primary and secondary prevention services. As a sexually transmitted disease that causes cervical cancer, HPV has significant implications for reproductive health. Consequently, the context of vaccine delivery and the target populations may be different from the traditional EPI milieu. Young women who may have initiated sexual activity only recently, or who are seeking family planning after childbirth, represent target populations for catch-up for both primary and secondary prevention for the following reasons:

- a positive experience with vaccination among this group will be a natural entry point towards the eventual vaccination of adolescents or pre-adolescents, especially this group's children;
- sexual and reproductive health programmes provide a broad range of services within a comprehensive approach to sexual and general health;
- sexual and reproductive health initiatives that reach out to older adolescents should address cervical cancer prevention;
- this group is the target of other interventions addressing sexually transmitted infections and most of the voluntary counselling and testing programmes for HIV; and
- nursing staff caring for this group are oriented towards preventing cervical cancer and most are trained in counselling.

It may be possible to implement simplified screening and vaccination programmes as part of an integrated reproductive health strategy to reach girls and women if a coordinated effort is made by all stakeholders. This would require synchronization with and timely inputs from programmes with experience in vaccine delivery, in sexual and reproductive health and in cancer control.

Health systems and policies

Considerations for introduction

The introduction of HPV vaccine into a national health-care system will raise questions for all countries. They will need to: use evidence to determine the age cohort to target, develop a service-delivery strategy, address the training needs of health professionals and other issues related to human-resource development, forecast the demand and supply of the vaccine, develop product-financing mechanisms and mechanisms for procurement and supply-chain management, and implement monitoring and evaluation programmes.

Evaluation of potential product financing and procurement mechanisms should be considered in the context of existing mechanisms used by organizations such as UNICEF, the GAVI Alliance, and the International Financing Facility for Immunization. The Global

Immunization Vision and Strategy provides opportunities for engagement because it highlights the importance of introducing new vaccines, extending them to other age groups and linking vaccines with other interventions.[45] Because global financing mechanisms for an HPV vaccine will depend on the cost of the vaccines, financing and procurement-related issues must be considered as soon as possible.

The role of supply and demand in ensuring equitable access

Manufacturing limitations for HPV vaccines are unclear. Without 5-year estimates of purchasing demand, the industry is unlikely to invest in building manufacturing capacity or move towards cost structures that include lower profit margins. A business case for HPV vaccine production and procurement that is specific to developing countries must be developed. Demonstration projects that will both inform industry using demand forecasting and provide models for introduction that maximize acceptability and access based on country-specific assessments are being implemented (J. Sherris, personal communication, 2006).

During negotiations on pricing structures, ministers of finance and purchasing agencies must not lose sight of the costs of service delivery. Ancillary costs, such as transportation and human resources (providers, educators and so forth), must be accounted for. Estimating these ancillary costs for cost–effectiveness models has proven difficult because they are country-specific. Countries must consider their pre-existing screening services, already functional school-based and/or expanded EPI programmes, and the comparable costs of other priority health interventions.

Conclusion

Cervical cancer is a unique public health challenge. It is gender specific, caused by a sexually transmitted virus, and primary and secondary prevention target opposite ends of a wide age spectrum. The natural history of cervical cancer has been studied in depth, and screening programmes that identify pre-cancerous lesions have been successful in significantly reducing incidence and mortality, albeit at a significant cost. Taken together, early vaccination of adolescents with screening and adequate evidence-based treatment could be components of a comprehensive strategy with the long-term goal of eliminating cervical cancer.

However, several knowledge gaps need to be bridged before HPV vaccine programmes can be introduced on a large scale, particularly in developing countries. Furthermore, even if the vaccines are introduced rapidly, screening and early treatment programmes will continue to be needed throughout the next several decades to prevent disease in women already infected or those who become infected with oncogenic HPV types not included in the vaccines.

There are critical issues of equity associated with introducing these new vaccines. International organizations, national governments and private foundations must address, at the highest level, how to minimize delays in accessing the vaccines in poor countries and to ensure access is equitable. Public spending on health is so low in those countries that have the greatest disease burden that external finance mechanisms to subsidize the purchase of vaccines will be necessary. These mechanisms may include advanced market commitments and long-term fund pledges through the International Financing Facility for Immunizations. Additional support from the GAVI Alliance to strengthen health systems should be garnered to facilitate introduction.[46]

We understand enough of the science and about the social issues to generate realistic prevention strategies. However, the challenge of delivering a vaccine that prevents both a sexually transmitted infection and cancer to an adolescent population will make it necessary to inform and educate not only adolescents but also their parents and the health-care providers who inform them. This must be seen as an opportunity, especially for the sexual and reproductive health community, given the need to educate adolescents early about risk-taking and general health. Health workers accustomed to wrestling with reproductive health concerns, both social and medical, are best prepared to be advocates for the HPV vaccine. Ultimately, each country will have to determine which parts of its health system have the capacity to implement effective and maximally efficient services.

Current adolescent vaccination programmes usually provide only single-dose boosters, for example, of tetanus toxoid and diphtheria-containing vaccines, and the three-dose HPV vaccination series represents a challenge; but it is also an opportunity to strengthen adolescent vaccination services. The HIV/AIDS community recognizes that introducing an HPV vaccine may provide a platform for the introduction of an AIDS vaccine in the future, given the probable need to vaccinate the same target population of adolescents. Introducing the HPV vaccine will also provide a test case for acceptability and a unique opportunity to reach out with important health messages to an often neglected demographic cohort.

The challenge for policy-makers and opinion-leaders is to acknowledge lessons learned from prior initiatives to introduce vaccines, and to ensure that this gender-specific disease has the necessary priority on the global public health agenda. High-level advocacy and a partnership among immunization, cancer-control and the reproductive health sectors must emerge to ensure that the right initiatives are implemented rapidly to prevent this disease that characterizes health inequity today. ■

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Résumé

Garantir l'accès aux vaccins HPV grâce à un système de services intégrés : point de vue de la santé génésique

En 2006, un vaccin quadrivalent contre le papillomavirus humain (HPV) a été homologué et un autre vaccin de ce type pourrait l'être aussi prochainement. On sait encore peu de choses sur les aspects pratiques qui devront être pris en compte dans la conception et la mise en œuvre des programmes de prévention du cancer de l'utérus intégrant la vaccination comme moyen de prévention primaire. Bien que ce vaccin puisse à terme être indiqué pour les individus des deux sexes, les jeunes filles, c'est-à-dire les filles et les femmes de 9 à 25 ans, seront les premières candidates pour la vaccination. Ce document présente les canaux de délivrance des vaccins HPV et les lacunes dans les connaissances critiques et devant être comblées pour que l'on dispose d'un support pour l'élaboration des futurs programmes de santé sexuelle et génésique. Il expose le rôle de soutien que la communauté des professionnels de la santé sexuelle et génésique, en collaboration avec les programmes de vaccination et de lutte anticancéreuse, pourrait avoir dans l'introduction des vaccins HPV dans le contexte des systèmes de santé actuels.

Resumen

Garantizar el acceso a las vacunas contra el PVH mediante servicios integrados: una perspectiva de salud reproductiva

En 2006 se autorizó una vacuna tetravalente contra el papilomavirus humano (PVH), y dentro de poco se podría autorizar otro tipo de vacuna. Poco se sabe sobre las consideraciones prácticas que fundamentan el diseño y aplicación de los programas de prevención del cáncer cervicouterino que incluyen la vacunación como una medida primordial de prevención. Aunque la vacuna podría estar indicada a la larga tanto para los hombres como para las mujeres, los candidatos iniciales a la vacuna serán las niñas, o las muchachas y mujeres de 9 a 25 años. En el presente documento se describen los medios que pueden emplearse para administrar las vacunas contra el PVH y las lagunas de información que habría que colmar para orientar los futuros programas de salud sexual y reproductiva. Se apunta el papel que podría desempeñar la comunidad de salud sexual y reproductiva, junto con los programas de inmunización y lucha contra el cáncer, en apoyo de la introducción de las vacunas contra el PVH en el contexto de los actuales sistemas de salud.

ملخص

ضمان إتاحة لقاحات فيروس الورم الحليمي البشري من خلال الخدمات المتكاملة: منظور الصحة الإنجابية

تم إجازة لقاح فيروس الورم الحليمي البشري الرباعي التكافؤ في عام 2006، كما سيتم إجازة لقاح جديد عما قريب. والحق أننا لا يتوفر لدينا سوى القدر اليسير من المعلومات عن الاعتبارات العملية الخاصة بتصميم وتنفيذ برامج الوقاية من سرطان عنق الرحم من خلال اللقاحات، كوسيلة أولية للوقاية. وبالرغم من أن اللقاح قد يوصف للرجال والنساء في نهاية المطاف، إلا أن اللقاح سيُعطى أول ما يعطى للفتيات، وصغار الفتيات، والنساء ممن تـتراوح أعمارهن بين سن التاسعة والخامسة والعشرين. وستـتناول هذه الوثيقة توضيح سُبُل تقديم خدمات التطعيم بلقاح فيروس الورم الحليمي البشري، وسد الفجوات المعلوماتية حتى يُستهدي بها في وضع برامج الصحة الإنجابية والجنسية في المستقبل. كما تقترح الدور الذي قد تضطلع به البرامج المجتمعية المعنية بالصحة الإنجابية والجنسية، وبرامج التمنيع ومكافحة السرطان، لدعم إدخال لقاحات فيروس الورم الحليمي البشري في سياق النظم الصحية الراهنة.

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