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Information brief on the new Human Papillomavirus (HPV) vaccine

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1 Executive Summary

The genital infection with human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Nearly all genital cancer cases in women are linked to this infection. Over 90% of these cancers occur in developing countries, where cervical cancer is the most common cancer in women. The vast majority of related deaths occur in developing countries.

An HPV infection can lead to precancerous lesions, which can be detected by screening programmes and usually successfully treated at an early stage. Such services, however, are nearly inaccessible to the vast majority of poor women in resource limited settings.

It is therefore of particular significance for developing countries that two vaccines which, when administered to adolescent girls and young women before their sexual debut, have recently been registered. They have shown a very high effectiveness in preventing infection with the virus. While there are remaining questions around the long term population effect of the vaccination on preventing ultimate cancer cases and about the duration of protection by the vaccine, many industrialised countries, including Switzerland, recommend the vaccination for adolescent girls and some have started to fund public vaccination campaigns. However, at a commercial price of around 600 US\$ for the vaccination, costs remain prohibitively high for developing countries. Other challenges are linked with health systems aspects linked to information campaigns, distribution, human resources, infrastructure- but also competing public health priorities and questions related to social acceptance. For middle income countries, which do not qualify for financial help from international partnerships such as GAVI, an important equity problem could arise around the HP vaccine. At the same time, when properly introduced system-wide and as part of a comprehensive cervical cancer control strategy, the vaccination could have many beneficial effects in strengthening the health systems in developing countries.

This is why an increasing number of public health and multilateral organisations have started to unite with civil society and the private sector around the “Global Call to Stop Cervical Cancer” to advocate for equitable access to this vaccination.

2 What is the human papillomavirus (HPV)?

The genital infection with human papillomavirus (HPV) is the **most common viral infection of the reproductive tract**. This sexually transmitted infection has its peak incidence in male and female **between the ages of 16 and 20 years** and it infects the skin or mucosal cells in the genital area of men and women (skin of the penis, vulva and anus, and lining of vagina, cervix and rectum). The infection **affects women and men differently**, as **most cases of infection progressing to cancer appear in women** (in the cervix). The infection is affecting men mainly with cell abnormalities, which are not necessarily detectable, but highly transmittable. **Condoms do not offer optimal protection**, as the transmission is from skin to skin, which is not necessarily covered by the condoms.

The very common HPV infection **usually resolves spontaneously**, but in certain cases it may persist and **precancerous cervical lesions may follow**. Factors favouring the development of lesions are immune suppression, multiparity (having been pregnant more than once), early age at first delivery, cigarette smoking, long-term use of hormonal contraceptives, and co-infection with two other pathogens leading to infection of the reproductive tract, Chlamydia trachomatis or Herpes simplex virus. **The lesions can be diagnosed and treated at this stage** (with cryo-therapy). However, if **untreated**, the infection and lesions **may progress to cervical cancer** over a period of 20-30 years. Virtually, **all cervical cancer cases** (99% according to WHO and UNFPA in 2006) are **linked to genital infection with HPV**.

There are dozens of **different genotypes of HPV**. High risk genotypes (HPV 16 and 18¹), are responsible for the majority of HPV-related cancers and low risk genotypes (HPV 6 and 11) can cause a substantial proportion of cell abnormalities, are responsible of significant morbidity. Cervical cancer is the second most common cancer in women worldwide. HPV is estimated to cause about half a million new cancers every year, with **over 90%² of cases occurring in developing countries, where cervical cancer is the most common cancer in women**. Over **250'000 women died of cervical cancer in 2005 – the vast majority in developing countries**. The high prevalence of cervical cancer in developing countries can be explained, in part, by the fact that the main intervention to prevent this cancer is treatment following the detection of precancerous cervical lesions via screening (traditionally by Pap smears). Establishing such **screening programmes as routine remains a challenge in low-resource settings**, and therefore the treatable precancerous phase is often passing without being detected. **Most women affected by cervical cancer in developing countries die of it without having access to any appropriate diagnosis, treatment and care**.

¹ According to sources and years of publications, others high-risk genotypes can be mentioned. Also, the total number of HPV genotypes can differ. We are here taking the values of WHO (2007).

² Different proportions according to sources (ranging from 80% to over 90%)

3 What is the HPV vaccine?

Two HPV vaccines have **recently been licensed**. **The vaccines are designed to prevent infection** and disease due to the respective genotypes. The first vaccine was quadrivalent (active against 4 genotypes 6,11,16 and 18) and a new one is bivalent (active against two genotypes 16 and 18). The immunisation comprises a series of three 0.5-miligram intramuscular injections over a six-month period. **The HPV vaccine is aimed at girls and women before their sexual debut** (between 9 and 26 years), as it is a prophylactic vaccine, and is not designed to treat persons who have already been infected with HPV. No recommendations for the use of the vaccines in men are available yet, but there are prospects for expanding the vaccines to boys in the future.

The HPV vaccine trial have shown very high preventive effectiveness against a virus infection and moderate precancerous cervical lesions (88-100%, with 95% confidence interval)- when, and this is important, the vaccine is administered to girls before they are exposed to the virus. According the WHO and UNFPA (2007), **girls should be vaccinated before their sexual debut to have the greatest impact, and this, without previous screening for HPV.**

However there remain **unanswered technical questions** about this vaccine:

- The trials inform on the efficacy of the prevention on the precancerous cervical lesions phase, and not on the prevention of cervical cancer itself. As the progress from one to the other can take 20 to 30 years, monitoring the overall effects poses a challenge to the vaccine advocates, policy makers and manufacturers alike.
- The duration of the protection is not yet known beyond five years after vaccination
- For the moment the cost of the vaccine is prohibitively high, posing also challenges to introduction in European countries. Innovative ways to finance its introduction that include international as well as private-public partnerships need to be established in the interest of reducing inequities in access to an important new preventive tool. "The world cannot afford to wait for new HPV vaccines and screening tests to eventually trickle down from wealthy countries to developing countries", where women need it most. (Dr Pablos-Mendez of the Rockefeller Foundation).

Australia has a government funded programme offering vaccination to girls age 12-26. Introduction of state funded vaccination is also considered in Canada. In July, the European Committee for Human Medicinal Products recommended the vaccine for **sale and marketing in the European Union** (IPPF news, 21.8.07). By March 2007, four European governments (Austria, Germany, France and Italy) have issued policy decisions, however, only Italy had agreed at that time how to fund it (Raffle,2007).

4 What perspectives for developing countries?

Cervical cancer is an **important public health issue for developing countries**, both because of its burden of morbidity and mortality and the fact that it is a preventable and treatable cancer. Lower socio-economic groups are at the greatest risk of developing cervical cancer. However, **in low-resource and middle income settings, the secondary prevention** of identifying and treating precancerous lesions before they progress to cervical cancer **is difficult** because the most efficient tool – the Pap smears – require microscopic exam by well-trained professionals, expensive infrastructure and more than one visit which is prone to loss in follow-up. An alternative technology has been developed for low-resource settings, the **visual inspection with acetic acid & naked eye (VIA)**. This tool is inexpensive, can be performed by non-physicians and in unsophisticated settings and requires one consultation for diagnosis and treatment if needed. However, its effectiveness in detecting abnormalities is lower as with Pap smears, and the International Agency for Research on Cancer (IARC) states that the evidence is not sufficient to recommend its adoption as primary screening test. On the other hand, a case study on VIA screening in India found VIA to be “a simple, affordable, safe, acceptable, and accurate test”³. They acknowledge at the same time that this technique is highly provider dependent, needing well trained staff and continuous quality assurance and monitoring to bring reproducible results with the sensitivity and specificity level described in the study. The position of WHO on visual screening is that it should be used where other screening methods are not possible due to low-resources settings. WHO has issued guidelines on how to perform the VIA⁴. For the future, there is also hope based on another screening methodology- **HPV testing**. This technique would not bring the disadvantages in terms of subjectivity and low reproducibility of the results linked to the VIA screening. The cost of the currently available test, however, is prohibitive for developing countries. A simple, affordable and rapid test that could bring results within 3 hours, is user friendly and accurate is currently being evaluated and could be available for use in developing countries soon. However, making this simple test available will not automatically translate into reduced mortality, since all the other programmatic steps related to coverage, good quality treatment, follow-up and monitoring need to be ensured to achieve such results³.

Due to those screening issues, the **solution that HPV vaccine can offer to developing countries is seen as a major improvement on decreasing the burden of HPV infections that lead to cervical precancerous lesions**. The **main issue** seen by WHO and UNFPA remains linked to **cost-effectiveness**. If a two-dose schedule could be used, or if HPV vaccines could be given at an earlier age (i.e. at the same time as other vaccines), the delivery could be greatly facilitated. However, for the moment, the safety of vaccination in girls below 9 years of age and possible interactions with other childhood vaccines have not been established.

Another issue is, that –like in developed countries- **the cost of a vaccination programme is not only composed of the purchase cost of the vaccine**, but

³ Rengaswamy Sankaranarayanan *et al* (2007)

⁴ http://www.who.int/reproductive-health/cancers/cervical_cancer_prevention_control_programs_p3.pdf

also includes costs of information and education, staffing, logistics and information technology infrastructure needed for the delivery. While for developed countries there is evidence that HPV vaccination campaigns in pre- and adolescent girls could be cost effective, the same may not hold true for the most impoverished countries. The virus genotype distribution causing cervical cancers in developing countries is different and less of these cancers go back to an infection with the currently vaccine preventable HPV 16/18 lesions (Mauri et al 2007). It **remains to be established, whether the currently available vaccines show the same effectiveness in developing countries**. Also, the **cervical cancer burden** will have to be **balanced** when making public health decisions in resource constrained settings **against other health and reproductive health priorities**, such as maternal mortality or malaria, which take a considerably higher toll on premature deaths and years of healthy life lost to disability.

On average, **it takes 10-20 years from the time a new vaccine is licensed until it is introduced in the public sector in the world's poorest countries**. The HPV vaccine faces the same obstacles as other vaccines (e.g. affordable price, securing sustainable financing, promotion and awareness campaigns, developing the infrastructure and training the health staff, etc) but also a specific one related to the sensitivity of the link to adolescent sexuality.

In addition, delivering this vaccine to 10 to 14 year old girls poses a new challenge to health systems in developing countries- **finding the girls**. Reproductive health services in these countries are usually little youth friendly and these providers have limited knowledge on transporting, storing and providing vaccines. Recruiting girls from schools will only be possible in countries where a majority of girls continue education beyond the primary school level.

The findings of currently ongoing **vaccine demonstration projects** led by PATH in India, Peru, Uganda and Vietnam are expected to be published in 2008 and are therefore eagerly awaited. (Cohen 2007)

There are also **issues around the social acceptance of the HPV vaccine**. As it targets girls before their first sexual intercourse and aims at assuring protection against a sexually transmittable infection, it touches upon subjects which are **highly sensitive in many societies**. For example, in the United States, a great debate is ongoing as to whether the HPV vaccine should be promoted by the government with conservative voices opposing this on the grounds that such a policy might encourage unprotected sexual activity on the part of teenager girls⁵. This question of social acceptance can be expected to form a further challenge in many developing countries – especially where premarital sex in women isn't tolerated for religious or other reasons, even though the realities may be significantly different.

Finding creative ways to deliver HP vaccine in developing countries, however, could have significant other benefits for the health system as a whole. **It could result in building synergies among immunisation, cancer control and sexual and reproductive health- and making these services more youth-friendly**. Close collaboration with the HIV prevention efforts would also be beneficial.

⁵ Brown David, « HPV Vaccine Advised for Girls », in *Washington Post*, Friday, June 30, 2006, p. A05. <http://www.washingtonpost.com/wp-dyn/content/article/2006/06/29/AR2006062901900.html>, visited August 16, 2007.

Internationally, an **increasing number of public health and multilateral organisations** (e.g. WHO, UNFPA, etc), foundations (such as the Bill and Melinda Gates or the Rockefeller Foundation), NGOs (International Planned Parenthood Federation) **and civil society are reuniting forces to advocate for political leadership and a prioritisation of cervical cancer in international and national development and health budgets.**

These actors are being joined by the **Private Sector** and a first international partnership agreement has been announced on this subject. In September 2007, the Merck Company announced that it will donate at least three million doses of its human papillomavirus vaccine “Gardasil” to developing countries. Merck said it plans to partner with a nongovernmental organization to establish a program to distribute the vaccine over the next five years, aiming for **one million women to be vaccinated.**

The **GAVI Alliance**⁶ will play a critical role in the vaccine’s affordability in the world’s poorest countries. This international partnership combines public and private sector resources to strengthen health systems and bring the benefits of immunisation to those in greatest need. Later this year, GAVI will make a determination as to the HPV vaccine’s priority among the many important vaccines already in the pipeline. (Cohen 2007).

It is interesting to note that it may be the **least developed countries** that see great benefit from HPV vaccination because they **qualify for financial help in implementing immunisation programmes from GAVI and so-called preferential tiered pricing from industry.** In terms of achieving the necessary price reduction to make the HPV vaccine an affordable option, the situation may be **more problematic in middle income countries**, such as Brazil, Mexico or India as they are not eligible for financial help from the alliance. In medium income countries, as long as the cost of the vaccination remains that high, this may result in a situation where the more affluent few get their daughters vaccinated in the private sector, while all the others need to wait for a long time to see the vaccination offered through the public system. This might **further increase inequities in sexual and reproductive health** in these countries (Franco, 2007).

A coalition of leaders at the World YMCA International Women’s Summit in Nairobi announced in June 2007 the launch of the **“Global Call to Stop Cervical Cancer”**. It is important to stress that efforts should not only be targeted at making the new vaccine available to girls and young women in developing countries, but to give the access to a **comprehensive and integrated sexual and reproductive health package** that **includes** other lifesaving technologies to prevent death from cervical cancer, such as **screening and treatment.**

⁶ <http://www.gavialliance.org/>

5 Data on HPV infection and vaccine in Switzerland

According to a fact sheet published by the Federal Commission for vaccinations, in Switzerland, it is estimated that **70% of women and men sexually active are infected once in their life by HPV. Every year in Switzerland, 5'000 women are diagnosed with precancerous cervical lesions, 320 women with cervical cancer** and a hundred die from it, although a yearly examination (that includes Pap smears) is reimbursed by the health insurance. Therefore, the **HPV vaccine is strongly recommended by this commission and the Swiss Federal office of Public Health**. A request has been sent to the Office of Public Health to include this vaccine in the vaccination package given in schools, and to have its costs – estimated in June 2007 at close to **600 US\$** – reimbursed by the health insurance. At the moment where this brief is written, the city of Geneva and the canton of Baselland (school health service) are examples of cantons that have started funding HPV vaccination for adolescent school girls. A **decision to finance the vaccination as part of the health insurance is pending, but expected to be taken within the coming weeks or months**.

The vaccination does not replace regular screening and public health efforts need to be intensified to **prevent a drop in screening discipline** based on a wrong sense of security after vaccination.

6 Relevance for SDC

As SDC needs to focus its strategic interventions and support in the field of health, promoting the **development and introduction of new vaccines is not considered a priority for SDC in its health policy**. SDC will therefore not become proactive, either in advocating or financing the introduction of the vaccine. However, since this is a new and rapidly evolving issue, **all SDC collaborators working in the health sector should keep themselves informed** about the current state of knowledge and discussion, as well as the potential opportunities opening up for developing countries. Once such a vaccine would be introduced into the EPI (Expanded Programme on Immunisation) schedule of a given country, it would of course be promoted as a part of the overall package. In the mean time, **SDC supported programmes working in the context of reproductive health** should be addressing the question of **screening and treatment for reproductive cancers as planned within the national policy and system** and as a part of an **integrated and comprehensive package of essential sexual and reproductive health care**.

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