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HPV vaccination

Cervical cancer is the commonest cancer cause of death among women living in developing countries, where 80% of new cases are diagnosed per year. In 2002 there were an estimated 493 000 new cases and 274 000 deaths from cervical cancer.[1] Yet, in developed countries that have implemented mass, organised cytology-based screening programmes, cervical cancer is a relatively rare disease.

For the past 60 - 70 years it has been well known that cervical cancer is preceded by an asymptomatic precursor phase (known as cervical intraepithelial neoplasia (CIN) and more recently as squamous intraepithelial lesions (SIL)) that, left untreated, will progress to invasive cancer in some women. It is now established that infection of the cervix with certain high-risk or oncogenic types of the human papillomavirus (HPV), particularly types 16 and 18, is essential in the pathogenesis of cervical cancer and its precursors.[2,3] Persistent infection of the cervix with high-risk types of HPV (of which 15 have been described) leads to the development of cervical cancer precursors (CIN or SIL) which are easily detected with the Pap smear. Detecting the precursors with the Pap smear and referring women with abnormal smears for colposcopy is known as 'secondary prevention of cervical cancer'. At colposcopy, where the cervix is illuminated and magnified after the application of acetic acid, if a significant precursor lesion is confirmed, the lesion may be removed, usually on an outpatient basis, under local anaesthetic. This prevents CIN or SIL from progressing to cervical cancer (a process that takes anything from 5 to 30 years).

Establishing and sustaining cytology-based cervical cancer screening programmes has, however, proved prohibitively complex and expensive for nearly all developing countries, hence their high rate of cervical cancer. HPV infection is spread by skin-to-skin contact, and the commonest route of transmission is sexual contact, although rarely vertical transmission from mother to child is also described. Until recently, primary prevention of cervical cancer relied on (*i*) abstinence; (*ii*) mutual monogamy of virgins; and (*iii*) condoms (which provided at best around 70% protection against transmission). Recently, however, two vaccines against HPV have become commercially available, providing us with the first really effective means of preventing infection with HPV and ultimately the development of cervical cancer.

The development of vaccines against certain types of HPV has been a major breakthrough in the options available for the prevention of cervical cancer. Monovalent (against HPV 16), bivalent (against HPV 16, 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium), and quadrivalent (against HPV 6, 11, 16, 18; Gardasil, Merck & Co., West Point, Pennsylvania, USA) vaccines have been tested in randomised placebo-controlled trials and shown to be safe, immunogenic and highly efficacious up to 6.5 years after vaccination. The vaccines use HPV type-specific L1 proteins that self-assemble into virus-like particles (VLPs). In the bivalent vaccine, the L1 protein of each type is expressed via a recombinant baculovirus vector. The vaccine consists of purified L1 VLPs of HPV types 16/18 formulated on an AS04 adjuvant comprising 500 µg of aluminium hydroxide and 50 µg of 3-dacylated monophosphoryl lipid A. The vaccine is delivered by intramuscular injection at 0, 1 and 6 months.

In the quadrivalent vaccine, the L1 protein for each HPV VLP type is expressed via a recombinant *Saccharomyces pombe* vector and the vaccine consists of purified L1 VLPs of HPV types 6/11/16/18 formulated on a proprietary alum adjuvant. The vaccine is also given via intramuscular injection, at 0, 2 and 6 months.

Both vaccines work by inducing neutralising serum antibodies (IgG). Studies consistently show that L1 VLPs induce high levels of serum-neutralising IgG, which is presumed to transudate across the cervical epithelium in a high enough concentration to bind to virus particles and prevent infection.

There is good evidence provided by randomised placebo-controlled trials that these vaccines prevent both persistent infection with the types included in the vaccines and pre-invasive lesions of the anogenital tract associated with the types present in the vaccines. In addition, the quadrivalent vaccine prevents the development of genital warts caused by types 6 and 11 (both associated with benign disease).[4-9]

Both vaccines appear to offer full protection against types 16 and 18, which are estimated to cause over 70% of cervical cancers worldwide, and a slightly lower fraction of cervical cancer precursors. There are some data indicating that the immune response to vaccination against types 16 and 18 provides some cross-protection against types 45 and 31, both important in the aetiology of cervical cancer, thus increasing the projected protection from vaccination to 75 - 80%.

However, both vaccines are prophylactic and should be administered to individuals before infection. As mentioned above, HPV is most commonly transmitted through sexual activity and is known to be the commonest sexually transmitted infection in the world. The vaccine should ideally be administered to girls (and possibly boys) before the onset of sexual activity, which varies considerably from country to country and in different cultures. Vaccination of girls aged 9 - 12 years of age with high coverage is probably going to be the most clinically effective and cost-effective strategy for cervical cancer prevention.

Goldie *et al.*[10] used modelling to predict that, assuming coverage of 70% of girls aged 9 - 12 years, vaccinating against types 16 and 18 will reduce the lifetime risk of cervical cancer by 43%. In addition, a combined approach of vaccinating young girls and screening women over the age of 30 years, at 70% coverage for both, will provide an estimated 53 - 70% reduction in the lifetime risk of cervical cancer. At coverage rates of 100% the expected cancer reduction with vaccination alone reaches 61%, but with the combination of vaccination and screening older women, the reduction is approximately 75%.

From a developing country point of view introducing the HPV vaccine into public health poses many challenges. The most obvious is cost, and the present price of both vaccines is unaffordable. However, cost is only one aspect. Firstly, no developing countries have established pubescent/adolescent health platforms or school health systems from which to vaccinate young girls (and possibly boys). This infrastructure will have to be created *de novo* and for this to happen, a great deal of political will needs to be generated. Unfortunately no studies have included infants, so neither vaccine will be approved for integration into the Extended Programme for Immunization (EPI) that has been successfully introduced into many developing countries, with high coverage. EPI is believed to save 3 million young lives per year.

Besides the need to create a new infrastructure, both vaccines require a cold chain and therefore a reliable source of electricity, which is notoriously difficult in many developing countries, particularly in Africa. The need for three injections and therefore follow-up poses its own challenges, as does the necessity for intramuscular injection (skills, medical waste disposal). Furthermore, one is injecting a young girl to prevent a disease that will only manifest after 30 years or more. Developing a national strategy will require those familiar with vaccination (paediatricians, public health officials) to communicate with those who work in the adult oncology field (traditionally two worlds that never intersect). However, developing a pubescent or adolescent health platform may be highly desirable. Such a platform would be a unique opportunity to offer parallel services to young people, e.g. booster vaccination against hepatitis B and tetanus, possibly anti-HIV vaccination in the future, anti-helminthic medication, nutritional assessment, and education about drug, tobacco and alcohol use, pregnancy prevention and sexuality in general.

Whether or not countries introduce the vaccine into the public health sector will be determined by (*i*) the burden of HPV-associated disease in a particular country; (*ii*) being able to convince politicians and health officials (particularly those who work with children and vaccination) that it is worth while to invest in vaccinating children to prevent a disease of adulthood; (*iii*) creation of the appropriate infrastructure for the administration of the vaccine; and finally (*iv*) cost. Clearly, implementing anti-HPV vaccination involves a great deal more than getting the needle in the arm!

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