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Vaccination for cervical cancer

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ABSTRACT Cervical cancer, one of the most common gynaecological cancers, is the consequence of persistent infection by the human papillomavirus family. This article is an authoritative review on the subject, by Professor IH Frazer, internationally acclaimed for his work on the development of the world's first cervical cancer vaccine.

KEYWORDS Cancer prevention, cervical cancer, vaccines, papillomaviruses

LIST OF ABBREVIATIONS Human papillomavirus (HPV), high grade squamous intraepithelial lesion (HSIL), World Health Organisation (WHO)

DECLARATION OF INTERESTS As the inventor of a technology that supports the HPV vaccines currently available, IH Frazer and his university derive royalties from their sale. He also consults in the HPV vaccine field for Merck, and for CSL.

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Cancer of the human cervix is a consequence of persistent infection of cervical epithelium by one of a limited number of members of the human papillomavirus family. This family of over 200 related viruses includes some which cause genital and body warts, with no apparent malignant potential, and many virus types which produce no apparent disease. However, a group of about 10 human papillomaviruses, particularly exemplified by HPV16, are termed high-risk viruses because persisting infection can lead to epithelial cancer of the anogenital epithelium, and contribute to about 20% of head and neck cancers and a small percentage of skin cancers.[1]

Infection with high-risk papillomaviruses is predominantly acquired through sexual intercourse, and occurs in at least 30% of young women and men, generally before the age of 25. Infection is common, largely because the lesion of acute infection is asymptomatic and persists for an average of a least a year. In consequence, HPV associated cancers are also common, contributing 10% of the total global cancer burden. Cervical cancer, the most common HPV associated cancer, kills 0·25 million women worldwide each year, and is one of the two most common causes of cancer death in women in most resource poor and developing countries http://screening.iarc.fr/cervicalindex.php?lang=1.

Most (>90%) high risk HPV infections of the anogenital skin resolve spontaneously. Resolution is likely to be immunologically mediated, as infection is more likely to persist in patients immunocompromised by HIV/AIDS[2] or through specific immunosuppressive therapy. Persistent infection is a prerequisite for development of cancer, and the determinants of persistent infection and of progression to cancer in immunocompetent adults are unknown. Cervical cancer prevention to date has therefore relied on screening for the cellular consequences of persisting infection with high risk human papillomavirus, through the pap smear program. Cytological screening is highly effective in appropriately resourced settings, although it relies on regular sampling, as a single cervical sample will identify cellular abnormalities predictive of cancer risk (HSIL) in only about 50% of subjects with prevalent high grade cervical intraepithelial neoplasia. Thus, HPV DNA testing has been added to the armamentarium of screening tests. The positive predictive value of this test, whether used alone or in conjunction with cytology, is low in younger women. However, the negative predictive value is high, allowing its use as a discriminator of risk in older women and as a test of cure following treatment.

Following the demonstration of a connection between high-risk HPV infection and cervical cancer in the early 1980s by zur Hausen and colleagues, there was considerable interest in developing vaccines to prevent and treat HPV infection. As papillomaviruses cannot be grown in tissue culture, these vaccines are based on recombinant viral proteins. While considerable interest remains in vaccines therapeutic for high-risk HPV infections, these are still in early stage clinical trials. Progress on prophylactic vaccines was facilitated by the demonstration in the early 1990s by several research groups, that the papillomavirus viral capsid proteins, when appropriately expressed in eukaryotic cells, can self-assemble into virus-like particles.[3] Commercial vaccines to prevent infection with high-risk human papillomaviruses (Cervarix, GSK; Gardasil, Merck/Sanofi

Pasteur) have recently become available, based on the virus-like particle technology. Production of these recombinant vaccines is similar to production of the currently available recombinant Hepatitis B vaccines.

As with all prophylactic vaccines, the HPV vaccines prevent infection through induction of specific immunity, and the likely mode of protection is induction of neutralising antibody directed against conformational determinants on the major (L1) virus capsid protein. Papillomaviruses are genetically stable double-stranded DNA viruses, and the L1 protein is generally conserved between HPV types. However, the major site of variability in this protein between viral genotypes is on the external surface of the virus, and HPV genotypes are therefore generally speaking immunologically distinct, requiring type specific vaccination for protection.

The current vaccines, which have been through a 15-year development process and clinical trials involving more than 25,000 young women in the developed and developing world, incorporate two high-risk HPV types, HPV16 and HPV18, which together are responsible for about 70% of cervical cancers. Gardasil also incorporates HPV6 and HPV11 virus-like particles, and can therefore protect against >90% of genital warts. In extensive clinical trials[4] (http://www.cdc.gov/nip/ACIP/mtg-slides-feb06.htm), these vaccines have been demonstrated to be ~95% effective at preventing infection with the HPV types they incorporate, and 100% effective at preventing HPV associated disease over a five-year follow-up period. Titres of neutralising antibody remain high at five years, with no evidence of declining levels with time.

The vaccines have proven safe and well-tolerated, with no vaccine attributable systemic adverse events or significant local reactogenicity, and appear also from a limited data set to be safe in pregnancy. There is no evidence that the commercial vaccines based on HPV virus-like particles have any therapeutic effect for existing HPV infections, nor that they adversely alter the natural history of high risk HPV infections, if given to people already infected. Thus, maximum benefit will come from delivery of vaccine programs to younger women before the onset of sexual activity, although women already infected with one HPV type will be likely to benefit from protection against infection with the other HPV types incorporated in the vaccine. An added benefit of early immunisation is that the immune response to this vaccine, as with many others, is best before puberty.

The HPV vaccines prevent infection only with the HPV types which they incorporate, though they may also give partial protection against two HPV genotypes (HPV45 and HPV33) most closely related to HPV18 and HPV16. Vaccination is, therefore, in countries where cervical cancer screening programs already exist, only one component of programs to prevent cervical cancer, though one that will prevent more than 70% of the surgery currently required to treat cervical pre-cancer. As such, treatment comes with a small risk of impaired fertility, and of postoperative bleeding, and mandates lifelong follow-up for recurrence, the socioeconomic impact of vaccination is nevertheless considerable. In resource poor settings, vaccination is likely to be the only measure available to reduce cervical cancer risk for the foreseeable future.

Vaccine efficacy data currently relate to women aged 16-26, with safety and immunogenicity data also available in 9–15-year-old boys and girls. Thus, most countries have licensed Gardasil in 9–26-year-olds of either sex, although some have restricted licensure to women only. Vaccine deployment, which requires three immunisations over six to twelve months, will require introduction of immunisation programs in age groups not currently targeted for repeated immunisations. Thus, introduction of a vaccine program to assist in preventing cervical cancer will require significant country-specific education of healthcare professionals, government, and the general public (http://www.who.int/reproductive-health/publications/hpvvaccines/index.html).

In addition, the substantial cost of the vaccines, together with the long period between introduction of a vaccine program and the clinical benefit through reduced incidence of cancer, will be likely to impact on vaccine introduction in resource-poor settings, though the combined effects of country-specific vaccine pricing, WHO program support, and funding from the Bill and Melinda Gates Foundation may speed up deployment in those countries that choose to accept this vaccine. More effective general deployment may come about through adding this vaccine to those delivered to infants through the expanded vaccine initiative – easier program delivery may offset the disadvantage of a longer time to impact on disease frequency.

KEYPOINTS

- Cancer of the cervix is a consequence of persistent infection of cervical epithelium by the human papillomavirus family.
- Infection with high-risk papillomaviruses is predominantly acquired through sexual intercourse, and occurs in at least 30% of young women and men, generally before the age of 25.
- Cervical cancer prevention to date has relied on screening for the cellular consequences of persisting infection with high risk human papillomavirus, through the pap smear program.
- Commercial vaccines to prevent infection with high-risk human papillomaviruses have recently become available. Production of these recombinant vaccines is similar to production of the currently available recombinant Hepatitis B vaccines.
- These vaccines have been demonstrated to be ~95% effective at preventing infection with the HPV types they incorporate, and 100% effective at preventing HPV associated disease.
- The vaccines have proven safe and well tolerated.
- Maximum benefit from delivery of vaccine programs is to younger women before onset of sexual activity, although women already infected with one HPV type will likely benefit from protection against infection with the other HPV types incorporated in the vaccine.
- HPV vaccines currently available have the potential to prevent the ~70% of cervical cancer caused by HPV16 and HPV18 infection, and are therefore an adjunct to, rather than a replacement for, whatever cervical cancer screening programs are currently available.

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