discontinuations before 6 months (RR 0.64; 95% CI 0.45 - 0.91) and overall adverse reactions (RR 0.51; 95% CI 0.36 - 0.73).[7]

## Comments

No randomised studies provide information on the optimal time for initiating prophylaxis in adults, or on when to stop prophylaxis. None of the trials included in the review focused on patients receiving treatment with antiretrovirals. Current studies neither report on the effects of prolonged co-trimoxazole use on bacterial resistance nor evaluate whether co-trimoxazole affects resistance of malaria parasites to sulfadoxine pyrimethamine (with which co-trimoxazole shares a component).

## Conclusions

Co-trimoxazole is highly effective in reducing mortality and morbidity in HIV-infected adults and children not receiving antiretroviral treatment. Similar benefits are seen in early and advanced HIV disease. Co-trimoxazole is well tolerated, with minimal side-effects. Further research is required on the optimal time for commencement of co-trimoxazole prophylaxis and to evaluate its use in patients on antiretrovirals.

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ISSUES IN PUBLIC HEALTH

# HPV vaccines: Bring me your daughters!

**Carol Thomas**

Our approach to cervical cancer prevention is set to change dramatically over the next decade with the advent of human papillomavirus (HPV) DNA typing, the probable demise of the PAP smear as we know it, and the registration of two highly effective vaccines against the two main HPV types (16 and 18). The latter account for about 70% of all cervical cancer cases globally and for 63% of those in South African women.[1] HPV-45 and HPV-31 account for another 10% of cases.[2,3]

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Except for a minority of non-mainstream, but remarkably visible and vocal, groups and individuals the general consensus worldwide is that HPV vaccines herald a new era and a phenomenal advance in the fight against cervical cancer, the most common cancer to affect women in South Africa and sub-Saharan Africa, where the established co-factors of smoking, long-term oral contraceptive use, HIV co-infection and high parity are also operative.[4] Lesotho has the unfortunate claim of the highest rate of cervical cancer in the world, with an age-standardised incidence rate of 61.6 (versus our 37.5) per 100 000 women.[5]

Women and health care providers have had to make two paradigm shifts around cervical cancer: firstly, although most HPV infections clear naturally, persistent infection with particular genotypes of a virus are responsible for most cases of cervical cancer (including the less common adenocarcinoma),[6] and secondly, close contact (as in both penetrative and non-penetrative sex) is the main mode of infection.

With an infective cause identified for cervical cancer and Jenner having led the way so many years ago, the logical next step was to develop a vaccine. In this case, antibody responses were elicited against virus-like particles (VLPs) resembling HPV capsid proteins. These HPV L1 VLP vaccines display significant immune memory.[7,8]

High-profile anti-breast cancer activism has ensured that women generally perceive breast cancer to be their main cancer threat. Within the private sector women primarily associate women's health visits with Pap smears, resulting in effective opportunistic screening and low rates of cervical cancer. Such screening, however, may lead to high rates of investigation and intervention in cases where HPV infection may not persist.

The dictum that prevention is better than cure is particularly relevant for cervical cancer. In the developed world cervical screening, independent of improving socio-economic factors, effectively decreases cervical cancer-associated morbidity and mortality,[9] but in developing countries where mass screening does not exist and any screening remains opportunistic, primary prevention could be the 'cure'.

The inability of lay persons *and* health service providers to understand the difference between mass and opportunistic screening and their goals has led to confusion and apparent lack of commitment by public sector health care providers. Pap smears are synonymous with an uncomfortable, invasive examination, hardly something women clamour for or deem worthy of chaining themselves to parliament gates for. Whether to spare women this examination or to deal more rapidly with large patient loads, health service providers may avoid performing these examinations. Although the syndromic approach to sexually transmitted infections has laudable intent, I believe it may contribute to the dissociation of the crucial speculum examination from the general gynaecological examination.

It is an accepted fact that the Pap smear as we know it would not make the grade if it were presented as a screening tool today. The search for appropriate screening strategies such as visual inspection of the cervix with acetic acid (VIA) with or without on-site treatment in under-resourced regions of the world continues, and these differ from country to country.[10] Immunisation is therefore the logical strategy, especially for our country and continent. There are, however, numerous barriers to this approach.

While the pharmaceutical industry has a right to recoup research and development costs and make an appropriate profit, we should remember that 20 years passed before hepatitis B vaccine was affordable to countries with the greatest need. Although hepatitis B vaccine offers protection against hepatitis B-related conditions, which include a cancer, HPV vaccines are the first to be developed with the sole purpose of preventing a cancer.

Pharmaceutical companies maintain that there will be tiered pricing to governments and that the cost of vaccines for large-scale immunisation programmes will be negotiable. Whether the lowest negotiable price will be affordable to South Africa remains to be seen. However, before negotiating with the industry, government needs the political will to impact on the disease burden of our most vulnerable women.

South Africa is one of the first African countries to register the vaccines, which are now available in the private sector. If medical aids do not pay for HPV immunisation, the cost will be entirely borne by individuals, mainly parents of adolescents. Injections are given at 0, 1 and 6 months, and the VAT exclusive exit price of the GlaxoSmithKline vaccine is R700 per dose. Add to this the cost of parental education, explanation and reassurance to patients, obtaining a prescription (schedule 4), consent from parents (as in Australia), access to follow-up, consumables and the very necessary cold chain (2 - 8ºC), which may be vulnerable to load shedding or inappropriate non-chilled transport by the patient herself, and it is evident that few providers are equipped to implement immunisation immediately. The optimal target group for immunisation falls just outside the usual paediatrician, general practitioner, immunisation nurse practitioner and gynaecologist's general domain. HPV immunisation would be imminently implementable by adolescent medicine units if they existed,[11] or by those with a special interest in adolescent and paediatric gynaecology.

The Global Alliance for Vaccines and Immunisation (GAVI) is a global health partnership of various funders to assist with immunisation coverage to resource-poor countries. To be GAVI-eligible a country has to have a gross national income of less than $1 000 per capita. This effectively excludes South Africa.

HPV immunisation as a national strategy to decrease the impact of cervical cancer will also have to compete with rotavirus and pneumococcal vaccines, the impact of which can be seen much more readily than preventing a cancer two decades later. It is encouraging that post-quadrivalent immunisation surveillance in the USA indicates that the abnormal Pap smear incidence dropped by 43% compared with non-immunised women in just 3 years, which translated into a 42% reduction in invasive procedures.[12]

From a national immunisation implementation point of view, although most of our girls attend primary school with attendance only dropping at secondary school level, and although immunisation coverage in South Africa is above 90%, there is no formal infrastructure to reach 'tweenies' and adolescents.

Now that cervical cancer is perceived as virally induced, there is also the danger of STI stigmatisation. Granny's cervical cancer as a reason for increased surveillance in her granddaughter tends to change to 'womb cancer' once the non-hereditary nature of cervical cancer is explained.

The introduction of the two vaccines has also spawned new terms like HPV-naïve and HPV-exposed. Neither is likely to inspire parents, who are expected to bring their young daughters for costly injections that will remove their 'naïvety'. The concerns of parents and the general public must not be underestimated or ignored. Because the vaccine is given to girls only, there may be perceptions around prevention of pregnancy and population control, permission or encouragement to become sexually active, and gender inequity. Both vaccines are registered for use in females only: the bivalent GSK vaccine is registered for females from age 10 onward, and the quadrivalent MSD vaccine is registered for females aged 10 - 26. Were there no cost constraints, and if we had adequate data on boys, one could argue that immunising all children would be desirable.

Although efficacy trials were aimed at young girls, immunobridging studies indicate that older women up to the age of 55 can be immunised against re-infection and new infections.[13]

Patients will have heard about the vaccines in the print and electronic media. To remain ahead, non-immunologists and non-vaccinologists are reaching for the books to jog dormant brain cells – how does the body respond to presented antigens? The virus manages to duck and dive the immune system because there is no viraemia and because the virus does not kill the keratinocytes of the cervical epithelium. Without cell death there is no inflammatory response, no pro-inflammatory cytokines, a meagre activation of epithelial antigen-presenting cells, and hence failure of natural infection to confer long-term protection or immunological memory.

To date (>5 years) the vaccine appears to produce lasting high antibody titres with no need for booster doses. Although the GSK vaccine has higher persistent antibody levels (ascribed to its ASO4 adjuvant system) than the MSD vaccine, the clinical relevance of this is unclear. The GSK vaccine shows good cross-protection against HPV-45 (78%) and HPV-31 (60%). Besides the vaccines against HPV-16 and 18, the MSD vaccine also contains vaccines against HPV-6 and 11, which cause 90% of genital warts.[14,15] The latter do not cause cancer, but may be picked up on cervical screening and result in increased investigation and treatment. Should government decide on an immunisation programme, the genital wart burden of morbidity, distress to women and cost of treatment to government will have to be factored in when choosing the most appropriate vaccine for a national strategy. Whether catch-up immunisation is going to be introduced also needs to be addressed. Ultimately, however, cost will probably be the deciding factor.

Because not all cervical cancer is prevented by the vaccines and because post-marketing surveillance is crucial, screening after immunisation cannot be eliminated. Whether this is by HPV typing or traditional methods is academic in the absence of national policy.

Due consideration must be given to oncogenic HPV-infected HIV-positive women in whom progress to cervical cancer is accelerated. We eagerly await the outcome of studies on HPV immunisation in HIV-positive women by Denny and others, and we should support national co-ordination and research initiatives like the Cancer Research Initiative of South Africa (CARISA).

Historically we have missed crucial opportunities to intervene in the HIV epidemic that is devastating our country. It would be unfortunate if we do not act to protect women, and thereby their families, from the impact of the HPV disease burden. We cannot be present when our adolescents have to negotiate safe sex, and can only hope that we have led by example and that they have developed adequate life skills to respond responsibly. We can, however, contribute to their long-term well-being by ensuring that we lobby for interventions like HPV immunisation and in doing so protect all women, especially the disenfranchised and those at most risk.


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