

Human papilloma virus vaccine – more than a vaccine

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Purpose of review

In February 2006, this journal summarized the scientific and psychosocial data generated about the first generation of prophylactic human papilloma virus vaccines. Since then, the world has held its breath, as the first vaccine to be aimed at the prevention of cancer has made its global debut. We look at this debut in the context of recent findings.

Recent findings

Many countries have embarked on vaccination programmes to target prevention and media attention has continued unabated. Studies show promising results regarding vaccine acceptance and cost-effectiveness. Who we vaccinate and the quality of campaign materials used now have the potential to alter the very effectiveness of these vaccines as primary preventive tools.

With the licensing of Gardasil a new era has started for patients and health professionals alike. Far from a passive new development foisted upon us, it promises to play a pivotal role: to optimize patient information and to advocate strategies we wish health policy makers to achieve.

Summary

We aim to summarize how updated information, since this debut, can add to our consultations and help give us a collective voice to address the rising healthcare disparities involved.

Keywords

cervical cancer, genital warts, prophylactic human papilloma virus vaccines

Introduction

Exposure to human papilloma virus (HPV) is a necessary precursor of cervical cancer [1]. Most HPV infection is cleared without any permanent sequelae but of those who will develop cervical cancer the average time to progression after HPV exposure is between 10 and 20 years (see Cancer Research UK webpage on cervical cancer risks and causes, www.cancerhelp.org.uk/help/default.asp?page=2755).

Worldwide, 470 000 cases of cervical cancer are diagnosed and about half of these will die of their disease. If we include other anogenital cancers and recurrent respiratory papillomatosis associated with HPV more than 500 000 cases of cancer are caused by HPV annually, with over 273 000 deaths attributable to cervical cancer worldwide. Roughly 70% of cervical cancers are caused by HPV types 16 and 18 [2].

The vaccine

The licensed HPV vaccine, Gardasil, is composed of the L1 protein of HPV types 6, 11 (causing 90% of genital warts), 16 and 18 (causing 68% of squamous and 83% of cervical adenocarcinomas) combined with an aluminium adjuvant. The quadrivalent vaccine is not therapeutic but prophylactic. It produces IgG antibodies to the HPV L1 protein of the respective HPV type epitope. IgG is the key antibody found in cervical mucus.

In all studies conducted to date, over 99% of study participants had an antibody response to all four HPV types 1 month after completing the three-dose series. High seropositivity rates were observed regardless of sex, ethnicity, country of origin, smoking status or body mass index. Data on immunogenicity and safety have been demonstrated for males aged 9–15 and efficacy studies are under way. The recommended age in females for vaccination is 11–12 but can be given as young as 9.

In those who have received all three doses the vaccine is 100% effective in protecting against cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma *in situ*, 98.9% effective against HPV type 6/11-related external genital warts and 100% effective against HPV 16 or 18-related vulval intraepithelial neoplasia (VIN) 2/3 or vaginal intraepithelial neoplasia (VaIN) 2/3 if the patient was not already infected with these types prior to vaccination [3].

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Abbreviation

HPV human papilloma virus

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Vaccination programmes: what is everyone else is doing?

Gardasil has been approved in over 76 countries worldwide including the USA, New Zealand, Canada, Switzerland and the countries of the European Union. France has recommended the vaccine for 14–23-year-old females, with reimbursement available via social security. Four large health insurers are now reimbursing for the vaccine in The Netherlands. Government funding is now available in Australia for Gardasil in 12–26-year-old females, where a national programme began to vaccinate all 12/13-year-old girls in April 2007, with catch-up for 13–26-year-old females. The UK hopes to begin vaccination of 12-year-old girls by 2008 [4*].

Mathematical modelling

Screening aside, vaccination alone may have the potential to reduce cervical cancer by up to 51%. Mathematical models have also been developed to predict the potential effects of vaccination on cervical cancer and genital warts in the context of an existing national screening programme [5**,6**,7*-9*]. These demonstrate how vaccination, with screening, can be cost-effective, suggesting reductions of over two-thirds of cervical cancer deaths, prevalence of precancerous lesions and incidence of genital warts, as achievable over several decades.

Predicted savings [5**] include: abnormal cytology tests (down by one-quarter), follow-up cytology tests, diagnostic tests (down by one-third) and treatments for precancerous lesions (down by one-third). Possible reductions in HPV epidemic dynamics have not been included into this particular model, so these may be underestimates.

The most influential parameter for cost-effectiveness is duration of vaccine-induced protection, currently showing no sign of diminishing at 5.5 years [10].

UK modelling [2] suggests that vaccinating closer to 14 years is more cost-effective than at 12 years. Although the absolute numbers of girls having sex under 14 years may be few, it is possible, however, that they are proportionately more likely to be the same girls who do not successfully complete existing screening opportunities; that is, the very girls whom we most want to protect.

A substantial part of the cost-effectiveness of vaccination programmes is in the prevention of genital warts. Genital warts have a worldwide prevalence of 0.6–3.0% [11**], with a rising incidence in men [11**,12*] and women, especially young people (see www.hpa.org.uk/infections/topics_az/hiv_and_sti/stidefault.htm). Even in a small country like the UK, a low estimate of the annual cost of treating genital warts is over £30 million. However, more accurate estimates are needed to allow for corporate financial costs, such as time off work for serial treatments,

and also for the amount of personal distress and relationship disharmony they cause. A study looking at the burden of genital warts in the UK is ongoing [4*], which should provide better estimates of episode lengths, costs and quality of life associated with anogenital warts, to inform future models.

Inherent to vaccination programmes excluding boys and men is a real possibility of disenfranchising the homosexual community, whose genital warts are just as real a burden and whose anogenital cancer is just as lethal. As models have not yet factored in for sexuality, they cannot predict how HPV vaccination may affect HPV pathology in homosexual men.

Actual vaccination coverage rates act in concert with other vaccination parameters and can gate the successful achievement of herd immunity. The benefit of vaccinating males as well as females is greatest at intermediate vaccine coverage (between 50–70%) and becomes increasingly important the lower vaccination coverage becomes, as was historically proved the case with rubella vaccination in the UK. This will be most significant for vaccination among older teenagers, whose vaccination coverage rates are expected to be at the lower end of the spectrum. Predicted incremental cost-effectiveness ratios of vaccination strategies, however, show just how big the extra financial cost could be of vaccinating males too (the model of Dasbach *et al.* [6**] predicts a cost of US\$4666 per quality-of-life year gained for females only, and \$45 056 for men and boys too).

Programmes targeting females only risk a potential socio-anthropological cost, as yet unquantifiable, of branding HPV, warts and associated cancers as a female-centred diseases. How can we expect our boys, men and sons to optimize condom use, as one type of primary prevention, without being involved in HPV vaccination as another? Whether or not this should be weighted over and above the short-term cost-effectiveness of vaccinating girls only is a question we should ask health policy-makers to answer.

Vaccine acceptability

Parental interest in the vaccine is high, with 70% acceptance rates or more across several strata of social and religious beliefs [13,14*,15*,16,17*]. Parental approval hinges more on perceived vaccine safety than its association with sexually transmitted infection. Other correlates of vaccine acceptance include [18*,19*,20**] perceived risk and severity of disease from the virus, knowledge of why vaccination in early adolescence is important, personal belief in vaccination and that others will approve of vaccination. Gleaned mainly from resource-rich countries these results cannot be extrapolated to other social milieux. Whether mothers, fathers or both act as key decision-makers in the approval process and whether this

differs for boys, girls or in different societies, is not yet known. Effective education campaigns will need to identify and address these key decision-makers.

Personal intention to receive the vaccine, in studies of girls and women, has been associated with the following factors [21[•],22[•],23^{••},24]: existing risk of exposure such as non-virginal status, previous sexually transmitted infection, history of an abnormal smear-test result, higher number of sexual partners and perceived support of parents/carers; endorsement by health professionals; inclusion of the vaccine in recommended vaccination schedules; low cost; and perceived vaccine safety.

Intent by males has begun to be studied and underlines their need too for information about HPV. Correlates of male vaccine acceptance included nonvirginal status, prior knowledge of HPV and origin from an urban area [25].

Disparity between medical and public knowledge

As scientific knowledge about the virus climbs to a high, the gap with that of the public continues to grow [26[•],27[•]]. That more than a quarter of women and half of men in surveys have never heard of HPV has changed little. For the moment, what makes a good story is not the same as what makes this a good vaccine.

Ethics

Cases may occur in which an adolescent wishes to receive the vaccine against the wishes of their parents [28]. These will need to be handled with the same ethical stringency as similar health issues for adolescents.

Education programmes

Education which can be individualized [29^{••},30] will allow for variations in background and acknowledge with respect the deeply held convictions or fears of parents who may initially refuse a vaccine. All parents should be made aware that the vaccine is simply more immunogenic before puberty. Education will also need to alleviate anxiety in those who may overestimate their individual risk of cervical cancer [31,32].

The diversity of modern media in which today's preteens are immersed [33[•]] presents both an opportunity and challenge. A tailored health platform for young adolescents, a group that is historically difficult to access, is needed. This could include other vaccines, such as for meningococcal infections, hepatitis B and rubella [34[•]], as well as other key health-promotion issues such as nutrition and physical fitness.

HPV infection is endemic in males and they are key to the success of primary prevention involving behavioural change. Although policy-makers and scientists await

efficacy data for boys, health professionals intuitively understand the benefits of educating boys and men from the beginning. It is essential that they are included equally in educational campaigns.

Health professional endorsement, essential for vaccine acceptance and provider variation [35[•]], needs good provider education.

Looking at the issue of vaccinating males shows how much existing provider attitudes can vary. In a survey by Medimix International [36], 75% of Australian physicians and 64% of Spanish physicians believed that boys should be vaccinated, quoting as key reasons: 'because they [boys] spread HPV as soon as they become sexually active'; 'Herd immunity' and 'Protection against genital warts and ability to spread the infection'. In the UK and France, however, 52% of physicians felt boys should *not* be vaccinated for reasons including: 'Not aware of research outcome', 'Not enough evidence as yet' and 'Too costly at present, no need if bulk of young women are vaccinated'.

We can build on existing knowledge about educating health professionals. For instance, hospital grand round lectures have shown to be more effective at influencing practice patterns for immunization than small-group in-service sessions [37].

Semantics and stigma

Sexually transmitted diseases, including HPV, are associated with high levels of stigma and shame [38[•]]. A recent study has shown that this can be effectively countered by informing women of the high prevalence of HPV infection, thus normalizing a distorted self-perception. It may be possible that normalizing how HPV is discussed in society may extend to the semantics of how we communicate about sexually transmitted infections in general. If such a process were driven by society's desire to gain adequate vaccine coverage, more widespread destigmatization of how sexually transmitted infections are discussed in our social fabric may also be possible.

Postvaccination surveillance

There is no evidence of protection against disease caused by HPV types with which females are infected at the time of vaccination, although there would be protection against disease caused by the other HPV types in the vaccine. As HPV typing is not part of routine screening, vaccination cannot as yet alter need for participation in the cervical screening programme.

Duration of protection has so far been followed for 5.5 years [10], but the duration of the antibody response is unknown. This is important as development of abnormal cells, which eventually lead to cancer, can take a long time.

Is it likely that ultimately the natural history of HPV disease will be changed by reducing the influence of types 16 and 18. There may be a shift in incidence of HPV infection by other types leading to cervical intraepithelial neoplasia and anogenital cancer. As multiple HPV types can act synergistically in cervical carcinogenesis [39] the vaccine may also be able to interrupt the carcinogenic potential of other oncovirus subtypes.

Healthcare disparities

Significant social disparities exist in access to cervical screening programmes across the world. Despite their effectiveness, HPV vaccines may not be able to further reduce the incidence of invasive cancers if these cannot be addressed. Accessing those who would most benefit from HPV vaccines is, perhaps, *the* key challenge currently facing our health planners [40^{••},41[•],42[•]].

Eighty-three per cent of cervical cancers are found in the developing world. Harnessing media attention can shine a spotlight on this disproportionate burden. Together we can have a powerful collective voice calling for enhanced provision for women with the least access to prevention.

Many approaches have been proposed [43[•],44^{••},45[•],46^{••}]. Both Merck and GlaxoSmithKline have suggested that they will discount the cost of existing HPV vaccines to such countries. The World Health Organization [47^{••},48[•],49[•]] has already endorsed vaccination as 'an ideal way to prevent HPV', but it could be another year before it can help the vaccines to be marketed in developing countries.

Some countries, such as India, in which 30% of all cancer deaths occur, may try to develop alternative low-cost HPV vaccines themselves. The International Alliance for the Prevention of Cervical Cancer, supported by the Bill & Melinda Gates Foundation, already has pilot HPV vaccination projects underway, including Uganda and Vietnam.

Conclusion

... it is not just having the knowledge, but using it.

Aristotle

Healthcare providers can play a pivotal role in facilitating the delivery of HPV vaccines as cost-effective primary preventive tools. The universality of HPV allows vaccination to act as a welcome arena, where sexual transmission may be discussed in a normalized and less stigmatized way. The vaccine has put a much needed spotlight on the health needs of adolescents everywhere.

Vaccination is also cost-effective for genital warts and is of direct relevance for men too. The challenge of how and

when to include males in education campaigns about HPV is a key issue, especially while current vaccination strategies exclude them.

Speaking with a collective voice we have the potential to extend the benefits of these vaccines beyond the individual in front of us. Embracing the potential to bring those presently outside screening into effective preventive programmes is a goal for which all of us can, and should, be proud to voice a current opinion about.

It is health that is real wealth and not pieces of gold and silver.

Mohandas Gandhi

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References and recommended reading

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 601–602).

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