

Should boys receive the HPV vaccine?

Many countries have implemented HPV vaccination programmes for girls.

Sam Hibbitts argues that they will not be fully effective unless extended to boys, but **Kate Cuschieri** says the benefit is insufficient



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YES A vaccination programme should target and stop transmission of the causative agent in order to prevent all associated diseases. The striking flaw in human papillomavirus (HPV) vaccination programmes is the focus on prevention of cervical cancer. What has been overlooked is that HPV infections are responsible for a range of non-cervical diseases in both sexes that have serious morbidity and contribute to a substantial healthcare burden. HPV vaccination of boys alongside girls would facilitate the eradication of HPV and protect boys from infection, reduce transmission, increase herd immunity, and effectively prevent HPV associated diseases. Limiting HPV vaccination to girls will not lead to eradication.

Benefits of HPV vaccination

Two HPV vaccines are available: Gardasil targets HPV types 6, 11, 16, and 18 and

Herd immunity obtained by vaccinating only women is likely to be insufficient to eradicate the targeted HPV types

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NO The burden of human papillomavirus (HPV) mediated disease is borne by women in the form of cervical cancer and its precursor lesions. Globally, cervical cancer is the second most common cancer in women, with an estimated 493 000 new cases and 274 000 deaths in 2002.¹ It is a devastating cancer with a peak incidence in young women in their 30s. HPV vaccines and associated immunisation programmes are hugely expensive, and including boys will double the cost for a small unjustifiable return. All efforts and resources must be channelled into ensuring high coverage rates are achieved and sustained in girls.

Two HPV vaccines are currently available: a bivalent vaccine that protects against infection with HPV 16 and HPV 18 (the types responsible for about 70% of cervical cancer) and a quadrivalent vaccine that also protects against infection with HPV 6 and HPV 11 (which cause around 90% of genital warts). Data from clinical trials indicate that both are highly effective in preventing incident infection with vaccine type HPV and associated genital

Cervarix targets HPV types 16 and 18. Gardasil has US Food and Drug Administration approval for use in males (9-26 years), and HPV vaccines induce an equivalent immune response in boys and girls. Preliminary studies of Gardasil and Cervarix in boys reported ≥99% and 100% seroconversion respectively at seven months, and both vaccines were well tolerated.^{1,2} Comprehensive efficacy data are expected to confirm that the vaccine can prevent HPV infection and associated disease in boys.

HPV vaccines are designed to target HPV specific infections. HPV types 6, 11, 16, and 18 are prevalent in both cervical^{3,4} and non-cervical diseases,^{5,6} and the vaccines can prevent a range of HPV associated diseases. HPV types 16 and 18 contribute to 30% of vaginal, vulval, and oropharyngeal cancers, 20% of oral cancers, and 80% of anal cancers,^{5,6} and the incidence of these cancers is steadily increasing. A US study to assess the burden of HPV associated cancers in men and women found an average annual incidence of 24 918 cases, with most (56.5%) being non-cervical: 2.4% were vaginal, 9.1% vulval, 12.1% anal or rectal, and 29.5% oropharyngeal or oral cavity tumours.⁶ In addition, HPV types 6 and 11 cause genital warts, which are a common sexually transmitted disease with

lesions. As a consequence, several countries have introduced HPV immunisation for young girls and women. However, even female only programmes are costly (estimated at £77m (€87m; \$130m) a year in the UK), and some would consider them excessive in countries that have robust screening and low cancer rates (at least at the current vaccine price).² Inclusion of males could be justified only if there were significant population benefits. This is not the case.

Some argue that immunising males will lead to enhanced herd immunity and consequently reduce rates of cervical cancer. However, the most consistent conclusion of the cost effectiveness evaluations is that vaccinating males provides only small additional benefit and is not cost effective,³ especially if female programmes obtain high (>75%) coverage. Such coverage rates are achievable—over 80% of adolescent girls have taken up the vaccine in national programmes in Australia and the UK.⁴ In resource poor settings, Kim et al (using Brazil as a model) concluded that at any coverage level, “A decision maker faced with the choice of trying to expand coverage in girls v boys should always increase coverage in girls first.”⁵

an estimated prevalence of 0.07-6.20/1000 women and 0.13-5.01/1000 men in the US.⁷ The primary objective of HPV vaccination should be to eradicate HPV infection, and this will be achieved only by a vaccination programme for both sexes.

Cost effectiveness

A US study evaluating the economic burden of non-cervical HPV disease calculated the overall medical costs to be about \$418m (£248m; €280m), range \$160m to \$1.6bn.⁸ More than 60% of this financial burden was attributable to treating genital warts, with non-cervical malignancies accounting for \$164.7m. Kim et al assessed the cost effectiveness of including boys in a routine HPV vaccination programme.⁹ Assuming 90% vaccine efficacy in males for HPV types 6, 11, 16, and 18 against all disease outcomes (cervical cancer, non-cervical malignancies, and genital warts) the ratio for a strategy including boys was \$90 870 per quality adjusted life year (QALY), which is below \$100 000 per QALY, the threshold for which an intervention is deemed a good economic investment in the US. If there was only 50% coverage in both sexes and lifelong vaccine efficacy against all disease outcomes, this ratio decreased to \$62 070 per QALY.⁹

Vaccinating males provides only small additional benefit and is not cost effective

Non-cervical disease

HPV is linked to other non-cervical neoplasms that affect men—namely, penile cancers, certain head and neck squamous cell cancers, and anal cancers. However, penile cancer accounts for <0.5% of male cancers worldwide and, unlike cervical cancer, has several independent causes, with HPV causing less than half of cases.⁶ As for head and neck cancers, the most potent risk factor is still smoking and alcohol consumption. The data on prevalence and attribution of HPV in head and neck cancers are conflicting, but a large study of 1670 cases found only 18% of oropharyngeal tumours were HPV associated.⁷ In addition, HPV associated head and neck cancers have a better prognosis than those that are HPV negative.⁸

Anal cancer is more similar to cervical cancer in that 90% of cases are attributable to HPV, but it is still comparatively rare. In the US, which has one of the highest rates, incidence is 0.9 cases per 100 000 population compared with eight cases of cervical cancer per 100 000 women.⁹ Moreover, an analysis of incidence in

One evaluation in the UK identified that if HPV vaccine induced immunity is short lived (10 years), a vaccination schedule that targets only 12 year old girls would not be cost effective unless high coverage was achieved.¹⁰ Other studies have shown that vaccinating the whole sexually active population would be more cost effective even when prevention of cervical disease is the only disease outcome.¹¹

Social inequity and psychological burden

Most cases of cervical cancer occur in low resource settings, and Castle and colleagues speculated that “targeting young women in these populations for HPV vaccination and screening older women would have a bigger effect on reducing the burden of cervical cancer than widespread HPV vaccination of young men from resource rich areas.”¹² However, this assumes that funding for HPV vaccination and decisions about implementation come from a central source. In reality, although policies and strategies for vaccine implementation in low resource countries are influenced by the World Health Organization Expanded Programme of Immunisation, local governments hold the final decision, which is driven by economic realities.

19 countries showed that in most, anal cancer is twice as common in women than men.¹ Men who have sex with men are at higher risk of anal cancer, but it would be more sensible to use targeted measures (such as anal screening) for this group than to try to vaccinate all boys. Furthermore, the effectiveness of the vaccine in reducing male neoplasms has not yet been proved in clinical trials.

Inequalities between the sexes regarding protection from genital warts apply only to countries that use the quadrivalent vaccine. Nevertheless, there have been understandable calls for genital warts to be factored into cost effectiveness analyses. Jit and colleagues’ economic evaluation that did incorporate the potential reduction of warts and non-cervical cancers still concluded that vaccinating boys was not cost effective.¹⁰ In the US, Hu and Goldie estimated the cost burden of non-cervical HPV associated disease to be 8%. This figure is not trivial, but does it warrant vaccinating both sexes when the other 92% is associated with the cervix?¹¹ A more recent analysis would indicate not—Kim and Goldie concluded that the inclusion of boys in the US immunisation programme would exceed “conventional thresholds of good value for money.”¹²

Herd immunity obtained by vaccinating only women is likely to be insufficient to eradicate the targeted HPV types. In situations where vaccine uptake in females is expected to be low, it is more cost effective to vaccinate males than vaccinate hard to reach females.¹³ A single sex HPV vaccination programme may also increase the psychological burden on women,¹⁴ and this sex inequality could amount to an additional healthcare burden that could be avoided if the vaccine was administered to both sexes.

Lessons from history

In 1996, the rubella vaccine programme for women was extended to cover men after the disease reappeared in men.¹⁵ Rubella and HPV differ in many ways, including mode of transmission. However, the rubella scenario shows the potential pitfalls of a single sex vaccine programme. I advocate making HPV vaccination available to boys and girls in order to eradicate HPV infection and associated diseases in the population.

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Boys still benefit

To believe that by vaccinating girls, only girls will benefit is naive. Smith et al assessed the impact of the Australian programme (in which girls receive the quadrivalent vaccine) on overall HPV infection rates and predicted a reduction in the age standardised incidence of HPV 16 infections of 56% by 2010 and 92% by 2050.⁴ HPV 16 is the most commonly detected type in male (HPV associated) cancer.^{16,9} Other, recent Australian data have shown a reduction of genital warts in both vaccinated women and heterosexual men.¹³ It is inevitable that lower rates of circulating virus brought about by vaccinating females will lead to a reduction in HPV associated disease in men over time.

There is currently no robust evidence to justify the expense and effort of vaccinating boys with existing HPV vaccines either in developed or developing countries. To do so would constitute a misuse of resources and a diversion from what should be the primary objective—vaccinating as many young girls as possible.

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