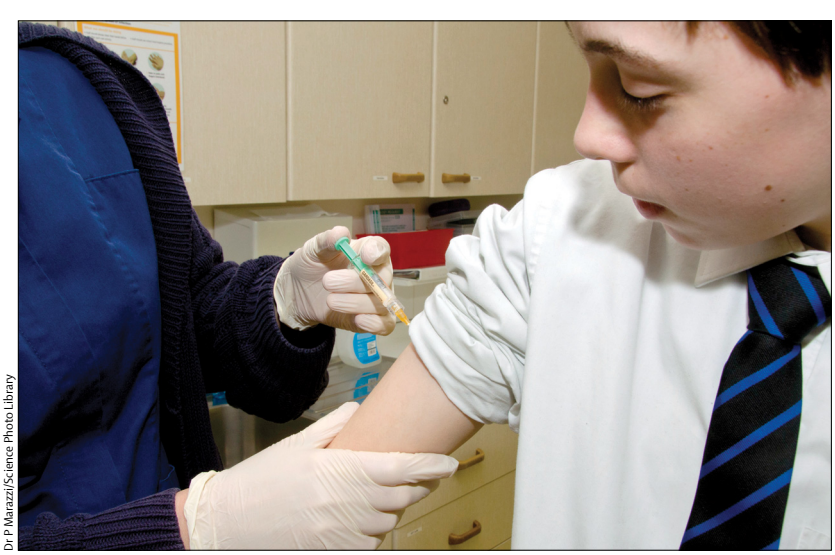
Expanding the benefits of HPV vaccination to boys and men

Human papillomavirus (HPV) is the most common sexually transmitted infection. It affects 80% of the population, with the initial infection usually occurring between 15 and 24 years of age. Persistent infection with high-risk oncogenic HPV genotypes, primarily types 16 and 18, is the cause of almost all cervical cancers.[1] HPV is also thought to cause about 95% of anal cancers, 75% of oropharyngeal cancers, 75% of vaginal cancers, 70% of vulvar cancers, and 60% of penile cancers.[2] Low-risk or non-oncogenic genotypes (eg, types 6 and 11) cause anogenital warts, low-grade cervical disease, and recurrent respiratory papillomatosis. In the USA, the incidence of oropharyngeal cancer in men now exceeds that of cervical cancer in women, and by 2020 the annual number of HPV-associated oropharyngeal cancers will exceed that of cervical cancers.[3] As a result, it is important to consider ways to expand our HPV prevention efforts to boys and men.

Available prophylactic HPV vaccines include Gardasil (Merck), a quadrivalent vaccine approved by the US Food and Drug Administration in 2006 that protects against HPV types 6, 11, 16, and 18;[4] Cervarix (GlaxoSmithKline), a bivalent vaccine approved in 2009 against HPV types 16 and 18;[5] and Gardasil 9 (Merck), a nine-valent vaccine approved in 2014 that offers protection against five additional oncogenic genotypes (types 31, 33, 45, 52, and 58) in addition to types 6, 11, 16, and 18.[6] The recommendations for vaccine administration vary slightly by country and vaccine type, but the primary target group is adolescents aged 9–13 years, with catch-up vaccination up to age 26 years. Importantly, these vaccines do not treat existing infection or disease and are therefore intended for individuals before initiation of sexual activity and exposure to HPV. Extensive studies[7,8] have shown these vaccines to be safe and not associated with increased sexual activity or earlier sexual debut among adolescents.



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Although it will take decades to show a reduction in HPV-associated cancers from the introduction of HPV vaccination, recent reports are encouraging. In March, 2016, the US Centers for Disease Control and Prevention reported a study[9] comparing HPV infection rates before (2003–06) and after (2009–12) the vaccine was introduced in girls who received at least one dose of the quadrivalent vaccine. The prevalence of HPV types 6, 11, 16, and 18 decreased by 64% in sexually active girls and women aged 14–19 years and by 34% in those aged 20–24 years. Previously, an Australian study[10] had shown that the proportion of girls and women, as well as boys and men, developing genital warts decreased significantly after the implementation of a national HPV vaccination programme in 2007.

However, despite the proven efficacy and safety of the HPV vaccines, uptake has been variable. In the USA, only 40% of girls and 22% of boys have completed the three-dose series.[11] Reasons for low vaccination rates include inadequate provider recommendations, parent opposition, few state-level mandates requiring HPV vaccination for school enrolment, and the absence of school-based immunisation programmes. In comparison, Australia, Belgium, the UK, and Canada have HPV vaccination rates exceeding 70% in girls (in both boys and girls in Australia), showing that high rates are achievable through national vaccination programmes. In low-income countries, GAVI has played a pivotal part in obtaining HPV vaccines at an affordable price and implementing national vaccination programmes. A prominent example is Rwanda, where more than 90% of eligible girls have undergone HPV vaccination.[12] However, many countries in sub-Saharan Africa do not have vaccination or screening programmes, and cervical cancer continues to be a leading cause of cancer-related death among women.

For boys and men, the scenario is different and needs our attention. Although cervical cancer has the highest HPV-associated cancer burden worldwide and is increasingly being recognised as a public health concern, other HPV-associated cancers, such as oropharyngeal, anal, and penile cancers, also result in substantial morbidity and mortality. Vaccination was not recommended for boys until 2011, lagging behind the recommendation for girls in 2006. Australia implemented a national vaccination programme for girls in 2007, which was subsequently expanded to include boys in 2012. In fact, most programmes worldwide do not include a recommendation to vaccinate boys, mainly because of cost and little recognition of an emerging epidemic of HPV-associated cancers in men. In the USA, 78% of HPV-associated cancers in men are oropharyngeal cancers.[2] The incidence of all oropharyngeal cancers is rising at 5% annually and has surpassed that of cervical cancer in women for the first time in 2010.[3] Similar trends have been reported in other high-income countries. At The University of Texas MD Anderson Cancer Center, the number of new oropharyngeal cancers is increasing at an alarming rate, from 98 cases in 1991 to 342 cases in 2012 (Sturgis EM, unpublished).

Unlike Pap and HPV testing for cervical cancer screening, no screening test exists for the detection of premalignant or early-stage oropharyngeal cancer. As a result, most patients present with advanced disease involving regional lymph nodes. Similarly, anal cancer rates are increasing in both men and women, with most patients presenting with locally advanced or metastatic disease. Because screening is not available or feasible for almost all non-cervical HPV-associated cancers, the incidence of HPV-associated cancers (chiefly in men) is likely to continue to rise until the present generation of vaccinated adolescents reach middle-age, translating to 30 years of an increasing burden of HPV-associated cancers in men. Primary prevention with HPV vaccination of both girls and boys has the potential to prevent this substantial burden. Further delays in expanding HPV vaccination programmes to boys, or allowing vaccination rates in boys to lag behind, will only mean greater suffering, loss of life, and financial burden.

The unprecedented progress in our understanding of the role of HPV in cancer and the development of effective and safe vaccines can decrease the HPV-associated cancer burden only if vaccination rates for girls and boys improve substantially worldwide. An aggressive stance on HPV immunisation and screening is needed to prevent the loss of countless lives from cancers that are largely preventable. Vaccinating girls and boys will lead to decreased HPV transmission rates and increased herd immunity, and will prevent not only cervical cancers but also other HPV-associated malignancies in both women and men.

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1 Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189:** 12–19.
2 Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst* 2013; **105:** 175–201.
3 Chatuvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011; **9:** 4294–301.
4 FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; **356:** 1915–27.
5 Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374:** 301–14.
6 Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015; **372:** 711–23.
7 Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine* 2011; **29:** 8279–84.
8 Bednarczyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics* 2012; **130:** 798–805.
9 Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV after introduction of the vaccination program in the United States. *Pediatrics* 2016; **137:** 1–9.
10 Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* 2013; **346:** f2032.
11 Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2014. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 784–92.
12 Binagwaho A, Wagner CM, Nutt CT. HPV vaccine in Rwanda: different disease, same double standard. *Lancet* 2011; **378:** 1916.