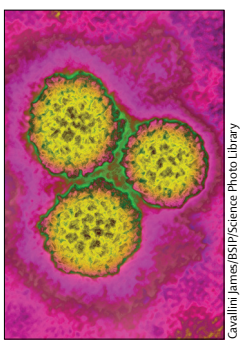
# Nine-valent human papillomavirus vaccine: great science, but will it save lives?



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In *The Lancet*, Warner K Huh and colleagues[1] report their final analysis of a randomised, double-blind trial of 14 215 women, aged 16–26 years, testing the quadrivalent human papillomavirus (qHPV; HPV types 6, 11, 16, and 18) vaccine compared with the nine-valent HPV (9vHPV; HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine. The women were recruited from 105 study sites located in 18 countries and received vaccination on day 1 and months 2 and 6. The 9vHPV vaccine consists of virus-like particles of HPV 6, 11, 16, and 18 (as found in the qHPV vaccine) and an additional five types, HPV 31, 33, 45, 52, and 58, combined with the adjuvant amorphous aluminium hydroxyphosphate sulphate.

In their first publication[2] of HPV infection and intraepithelial neoplasia in this group of women in 2015, the researchers reported that the 9vHPV vaccine prevented infection and disease related to the additional HPV 31, 33, 45, 52, and 58 and generated a non-inferior antibody response to HPV 6, 11, 16, and 18 compared with the qHPV vaccine. Furthermore, high-grade cervical, vulvar, or vaginal disease related to infection with HPV 31, 33, 45, 52, and 58 in a prespecified per-protocol efficacy population was 0·1 per 1000 person-years in the 9vHPV vaccine group compared with 1·6 per 1000 person-years in the qHPV group. Acknowledged as a limitation of the study was the absence of a placebo group, which the investigators justified on the basis that efficacy of the qHPV vaccine had been established in robust international clinical trials and it was considered unethical to use a placebo given this information. Few adverse events were reported in either of the trials, although women vaccinated with the 9vHPV vaccine reported more adverse events at the injection site.

These results have been confirmed in Huh and colleagues' current trial.[1] On the basis of epidemiological studies, it was estimated that the 9vHPV vaccine could prevent approximately 90% of cervical cancers, 90% of vulvar and vaginal cancers, and 70–85% of high-grade cervical disease in women, and approximately 90% of HPV-related anal cancers and genital warts in men and women worldwide.[3,4] The data reported in Huh and colleagues' paper convincingly show that prophylactic administration of the 9vHPV vaccine is highly efficacious in the prevention of HPV infection, abnormal cervical cytology, histopathologically confirmed high-grade anogenital tract disease, and cervical procedures associated with the HPV types included in the HPV vaccine. Efficacy was more than 95% for the 9vHPV vaccine in the per-protocol population, the prevention of cervical intraepithelial neoplasia grade 2 or worse caused by HPV 31, 33, 45, 52, and 58, and for 6-month persistent infection.[1] Nearly all participants (>99%) seroconverted to all nine HPV vaccine types.[1] The US Advisory Committee on Immunisation Practices recommended the 9vHPV vaccine as one of three HPV vaccines to be used for routine immunisation (the others being the qHPV and bivalent vaccines against HPV 16 and 18) at the ages of 11 years or 12 years ab initio, as well as girls and women aged 13–26 years and boys and men aged 13–21 years, and to age 26 years in men who have sex with men or immunocompromised people, including individuals who are HIV positive.[5]

Huh and colleagues' trial was designed to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine, and has succeeded in so doing; however, from a public health perspective, the key issues are cost-effectiveness, affordability, implementation of the vaccine with wide coverage of the target age group, functional health systems, and good adherence. In favour of the introduction of the 9vHPV is that a two-dose schedule has shown non-inferiority to a three-dose schedule in 9–14 year olds after two doses (administered 6 months or 12 months apart) compared with three doses in 16–26 year olds administered at months 0, 2, and 6,[6] similar to findings with the qHPV and bivalent HPV vaccines. Brisson and colleagues[7] compared population-level effectiveness and cost-effectiveness of 9vHPV and qHPV vaccination in the USA. Using a multitype, individual-based, transmission–dynamic model of HPV infection and disease, they found that switching to a 9vHPV gender-neutral HPV vaccination programme was likely to be cost saving if the additional cost of the 9vHPV is less than US$13.[7] Although the 9vHPV is likely to be cost-effective, whether it will be affordable, particularly for low-income and middle-income countries (LMICs) is not known.

To make an impact on HPV-associated disease, particularly cervical cancer, which is responsible for over a quarter of a million cancer-related deaths in developing countries, wide coverage of young women with HPV vaccination is crucial.[8] A number of studies,[9] which included countries supported by Gavi, the Vaccine Alliance, have shown that this can be achieved; however, a substantial amount of financial, logistical, and human resource support is required.[9] In countries in which secondary prevention of cervical cancer with screening has not been initiated or sustained in any meaningful way, HPV vaccination might be the only hope for prevention of HPV-associated diseases in the future. Introducing HPV vaccination into these countries will require major health-system strengthening, political will, and buy-in from national health agendas. Many of these countries also lack any infrastructure for treatment and support of cancer, which makes prevention crucial to having an impact on cervical cancer incidence and mortality. The extra protection provided by the 9vHPV is unlikely to make any difference to the lives of women in LMICs if access is limited by cost, logistical, political, and health-system constraints, despite attempts by many societal sectors to bring HPV vaccination to LMICs. It is essential that the international community pay attention to the gross inequities that exist in cervical cancer prevention efforts,[10] and although the research presented in this paper is robust, credible, and done to the highest standards, it might still be far from providing an intervention that will save the lives of women in LMICs.

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I declare no competing interests.

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