Preliminary HPV vaccine results for women older than 25 years

After prophylactic human papillomavirus (HPV) vaccination, cost-effectiveness models predict that a reduction in cervical cancer will occur decades from now, but only when 90% of all girls aged 11–12 years have been vaccinated for many years, assuming vaccines confer lifelong protection. Should prophylactic vaccination protect women for less than 15 years, the incidence of cervical cancer will shift to women older than 25 years, with no overall decrease in cervical cancers from early vaccination. Women older than 25 years would again be susceptible to oncogenic HPV types causing cervical cancer at the same rate as younger women, but now with seropositivity that is insufficient to confer immunity. Persistent HPV infections transcribe virions that repeatedly re-infect the genital mucosa. Prophylactic vaccination, however, could neutralise this auto-inoculation, reducing recurrent cancers over time. Long-term follow-up studies show that women with treated cervical intraepithelial neoplasia (CIN) have between three and 12 times the rate of redevelopment of new genital cancers over 10–20 years than does the general population. While we wait to see whether HPV vaccine efficacy will last more than 15 years, 93 million women worldwide have already been exposed to HPV 16 and 18. 83 000 women will develop cervical cancer every year despite ongoing organised screening programmes, and an additional 400 000 women per year in countries without screening will develop cervical cancer. Clearly, we need to understand the prophylactic benefit of HPV vaccines in women older than 25 years who fall into two groups: women without present HPV infections with low antibody titres (seropositive and PCR negative) and those naive to HPV 16 and 18 exposure (seronegative and PCR negative). Past work has clearly shown that the two commercially available HPV vaccines are prophylactic rather than therapeutic and will not hasten regression of present infections, or hasten their progression to invasive cancer.

In The Lancet today, Nubia Muñoz and colleagues report on the efficacy of the quadrivalent HPV vaccine for women aged 24–45 years, after 26 months of follow-up in populations in which black women were under-represented. Vaccine efficacy, ranging from 31% in the intention-to-treat population to 91% in a per-protocol population, was determined by a composite endpoint comprising cervical or external genital disease or type-specific infection that had persisted for at least 6 months, not the cancer-surrogate of CIN 2 or 3 disease. About 30% of women in the trial were seropositive and PCR negative for HPV 6, 11, 16, or 18, representing the population at highest risk for cervical cancer. But this group of women were not followed up for a sufficient time for HPV 6, 11, 16, or 18 persistent infection to progress into any grade of CIN disease.

Antibody titres maintained after 24 months, however, do allow immunobridging inferences of efficacy to younger populations (figure). The high anamnestic titres provide great hope that the available HPV vaccines will be at least partially effective in prevention of new and recurrent infections in seropositive women vaccinated at older ages.
The antibody titres correlating with the quadrivalent vaccine’s efficacy in seronegative and PCR negative women aged 24–45 years are consistent with past studies in women in other age-groups that used the surrogate endpoint of CIN 2 or 3 for longer follow-up. This shows a similarly generous antibody response in older women as in younger women for both the quadrivalent vaccine and the bivalent (HPV 16 and 18) vaccine. The peak neutralising antibody response for HPV 16 is two to four times higher for the bivalent than for the quadrivalent vaccine in women aged 24–45 years, still remaining more than a 100 times greater than the titres seen in naturally infected women of similar age for both vaccines.6,7,10–12 Similarly, the peak neutralising antibody titres to HPV 18 are seven to nine times higher for the bivalent than for the quadrivalent vaccine in women aged 24–45 years, still remaining more than 20-fold higher than is seen in naturally infected women of similar age for both vaccines.5,12 In this study of 24–45-year-old women, immunobridging links the quadrivalent vaccine efficacy against persistent HPV infection to the 5-year protection against CIN 2 or 3 reported in vaccine trials in 16–23-year-old women, implying that over 5 years women aged 24–45 years will have similar protection against CIN 2 or 3 as do younger women.5,12

Whether the quadrivalent HPV vaccine will provide a full 15 years of protection against cervical cancers caused by HPV 16 or 18 has yet to be shown. Should the duration of vaccine efficacy be greater than 15 years, prolonged increases in screening intervals approaching twice in a lifetime for vaccinated women would be possible. This change in screening interval could substantially decrease the cost of the organised screening programmes, in addition to the health benefits and cost savings associated with the prevention of new HPV infections and cervical cancers in young women and women older than 25 years. In the end, duration of vaccine efficacy, the crucial parameter in all cost-effectiveness analyses, determines whether widespread vaccination of women older than 25 years is a personal choice or a public obligation.

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