Balancing the cost–benefit equation for cervical cancer prevention: a moving target

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The arrival of new vaccines and new technologies for cervical cancer screening presents decision makers with a moving target for estimating the effect and associated costs of these measures for the prevention of cervical cancer. Publicly funded human papillomavirus (HPV) vaccination programmes have been rolled out in many countries.[1] The ability to provide primary prevention of cervical cancer has afforded these countries the opportunity to reassess cervical cancer screening guidelines in terms of technology, starting age, and frequency. Some countries are now considering a transition from conventional cervical cytology to HPV testing as the primary triage for prevention of cervical cancer.[2] These proposed changes are being considered concomitantly with the imminent arrival of the nonavalent HPV vaccine (HPV9), which provides protection against roughly a further 20% of cervical cancers over the current quadrivalent (HPV4) and bivalent (HPV2) vaccines. Australia has been at the forefront of this revolution in the management and prevention of cervical abnormalities and cancer and, from 2017, cervical screening will transition from 2-yearly cytology-based screening to 5-yearly HPV screening.[3]

In *The Lancet Public Health*, Kate Simms and colleagues[4] present the results of a cost-effectiveness analysis of HPV9 in the context of primary HPV screening in Australia. Cost-effectiveness analyses have been conducted for HPV9 in various settings,[5–8] and have shown that the predicted cost savings and gains in quality adjusted life-years (QALY) are largely attributable to reductions in the burden associated with surveillance and treatment of precancerous lesions, and thus contingent on the screening algorithm.[5,8] However, these analyses were not done in the context of primary HPV screening so, for countries considering this transition, Simms and colleagues' study is the first to provide an indication of cost-effectiveness of HPV9, albeit specifically in an Australian setting. A study by Kim and colleagues[9] took a somewhat different approach in that the aim was to identify the most cost-effective cervical screening strategy for US women already vaccinated with the HPV2, HPV4, or HPV9 vaccine.

Simms and colleagues estimate the incremental effect of HPV9 on the lifetime risk of precancer treatment, cervical cancer diagnosis, and cervical cancer death, as well as the maximum additional cost per dose of HPV9 over HPV4 at a willingness-to-pay threshold of AUS$30 000 per QALY. Both one-way and probabilistic sensitivity analyses were done for a wide range of scenarios. The approach is novel in that two separately developed and validated models accounting for HPV transmission, vaccination, natural history (including cervical precancer and cancer), and screening were used independently to do the analyses, and the findings compared. Whereas one model (Policy1-Cervix) was originally designed for evaluations in an Australian setting, the other (HPV-ADVISE) has been designed for Canadian and US settings, and was recalibrated for this study to Australian cervical cancer rates. Under base-case assumptions (for which there were differences between the models), both models showed that, in addition to the reductions in lifetime risk of cervical cancer and death attributable to HPV screening (>18% *vs* cytology) and HPV4 vaccination (a further >50%), a transition to HPV9 will provide a further 11% reduction in these outcomes. On this basis, Simms and colleagues estimate that for HPV9 to be a cost-effective replacement for HPV4 under the same sets of assumptions, the additional cost per dose cannot exceed AUS$23 (HPV-ADVISE) to AUS$36 (Polycy1-Cervix).

This study provides an important and valuable framework for decision makers to assess the cost-effectiveness of transitioning to HPV9 in combination with primary HPV screening for cervical cancer. Although the results reported are for the Australian setting, costs and other key inputs can be modified to enable the same analyses to be done in other settings. The study has several strengths, including the use of two independently developed models that provides a level of confidence in the robustness of the predicted outcomes, both of which incorporate dynamic HPV transmission components that account for herd immunity effects. But how widely applicable is this framework to other settings? The study by Kim and colleagues,[9] while focusing

on women already vaccinated, examines a range of alternative screening strategies and shows that the most cost-effective strategy might depend on several factors, including the proportion vaccinated, the vaccine used (HPV2, 4, or 9), the age of first screen, and the screening frequency. In another study,[10] that did not investigate the effect of vaccination, Felix and colleagues suggest that HPV RNA testing including genotyping for HPV types 16 and 18 (co-testing) might have greater effectiveness in reducing cervical cancer incidence and deaths at a lower cost than primary DNA-based HPV testing.

What is certain, as discussed by El-Zein and colleagues,[11] is that screening practices will evolve over time as cervical precancerous lesions become increasingly rare, to the extent that the harms of screening might eventually outweigh the benefits. Finally, the most cost-effective combination of vaccination and screening might not be the one that maximises reductions in cervical cancer incidence and death. Even if elimination of cervical cancer were possible, the measures required to achieve this are likely to be unaffordable. Ultimately, society should decide the price it is willing to pay for the prevention of cervical cancer.

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