Causal system modelling of cervical cancer screening

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Australia was one of the first countries to introduce human papillomavirus (HPV) vaccination and to show its favourable effects.[1] In a planned renewal of the Australian cervical screening programme, a comprehensive effectiveness and economic evaluation was done, based on literature review and simulation by a mathematical model. In *The Lancet Public Health*, Jie-Bin Lew and colleagues present the findings of this evaluation.[2] Their analysis included both unvaccinated and vaccinated cohorts and considered many options: the screening test and interval (eg, conventional or liquid-based cytology at IARC intervals [ie, every 3 years for women aged 25–49 years or every 5 years for women 50 years or older], or HPV testing [with or without cytology] every 5 years); management of screen-positive women; the age to end screening (64 or 69 years); and active invitation versus reminders. Although predictions were drawn for the Australian context and were compared with current Australian practice (cytology every 2 years for women aged 18–69 years), some conclusions are plausibly applicable to many high-income settings.

First, in unvaccinated cohorts, the HPV-based strategies were the most effective, which accords with findings of a pooled analysis of four randomised trials showing greater efficacy of HPV-based screening every 5 years compared with cytology-based screening every 3 years.[3] Second, strategies based on stand-alone HPV always showed the lowest predicted cost with respect to life-years saved. Third, these results were largely confirmed for vaccinated cohorts, for whom no comparable randomised trial data are available, although cervical cancer incidence and mortality were much lower in vaccinated cohorts (age-standardised rate, 2·17 and 0·53 per 100 000 women, respectively, with final guidelines) compared with unvaccinated cohorts (4·73 and 1·15 per 100 000 women, respectively, with final guidelines). Fourth, differences in the predicted cost per life-year saved between most of the strategies based on stand-alone HPV testing were smaller than were those between such strategies and the other modelled strategies.

A targeted sensitivity analysis, accounting for uncertainty of key variables governing the natural history of cervical cancer—eg, precancerous lesion progression and regression—and triage method performances, would allow direct comparison of the cost-effectiveness of the different HPV-based strategies. This analysis seems especially important for triage strategies, because no randomised trial has been done to directly compare them. Data show that, if triage-negative women repeat HPV testing after 12 months and those still HPV-positive are referred to colposcopy, as done in all the alternatives simulated by Lew and colleagues, then changes in criteria for immediate referral result in scant variation in the overall proportion of high-grade cervical intraepithelial neoplasia (CIN) detected on either occasion.[4] Thus, the difference between such triage strategies is mainly in the proportion of lesions detected with 1-year delay instead of immediately, and the effect on cervical cancer will depend on the progression rate of such lesions during the year. The relevant variables are related to natural history and to previous screening history and its sensitivity. For some variables (eg, progression to invasion), available evidence is sparse. Uncertainties about these assumptions can have a large effect on the relative effectiveness of different triage methods but little effect on the relative effectiveness compared with cytology-based screening, which depends largely on the relative sensitivity of HPV testing and cytology.

Efficient integration of vaccination and screening is currently another major issue in cervical cancer prevention, and the choice of screening intervals in vaccinated women is an important one. Lew and colleagues predict that moving from intervals every 5 years to every 6 years will increase cancer incidence and mortality by 3–4% and reduce costs by 8–10%, when keeping the same screening strategy, both within vaccinated and unvaccinated cohorts. However, predicted values for incidence and mortality in the vaccinated cohort are much lower than in the unvaccinated cohort. Prolonged intervals in vaccinated cohorts would be acceptable as long as they entail a cancer risk lower than the cancer risk of unvaccinated cohorts with current intervals. Resulting increases in screening interval could be much more than 1 year, even with vaccination against HPV16/18 only, but exactly defining the interval is not trivial. Extending vaccination age coupled with prolonged screening intervals was proposed to rapidly reduce cancer incidence.[5] At a consensus conference in Italy,[6] a suggestion was made to base the interval extension on the risk of CIN3 during follow-up noted in women

vaccinated for HPV16/18 in catch-up campaigns—ie, older than age 12 years—who are HPV-negative at age 25 years. Modelling could be very useful to define this extension. However, when predicting the effect of different screening intervals, assumptions on the natural history—eg, on the rates of progression from HPV infection to CIN3 and from CIN3 to invasive cancer—directly determine the result. Validation of models by comparing their predictions to known features seems important. An example (among many others possible) could be the predicted age-specific incidence without screening. Available data show no increase after age 40–50 years in unscreened cohorts.[7,8] Model predictions for the same situation should be consistent.

Overall, these examples show that modelling can be very useful to design and evaluate health programmes[9] but cannot overcome uncertainties in knowledge about the relevant variables, thus, integration with routine surveillance and field studies is needed.[10] Integration with randomised trials would be the best approach. The co-existence in Australia of population-based registries, accurate modelling approaches, and the Compass screening trial represents a unique opportunity.

For the **Compass trial** see http://www.compasstrial.org.au

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GR and IB acknowledge support from the European Community's Seventh Framework programme (FP7-HEALTH-2013) under grant agreement number 603019 (CoheaHr). GR acknowledges support by the Associazione Italiana per la ricerca sul cancro (AIRC) grant IG14119. IB acknowledges support from the Bill & Melinda Gates Foundation (grant number OPP1053353).

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