19TL4602
Population-level impact of human papillomavirus vaccination

We applaud the systematic review by Mélanie Drolet and colleagues[1] that provides compelling evidence of the substantial impact of human papillomavirus (HPV) vaccination programmes, and we hope it will influence policy makers.

However, the effect of vaccination in a population depends not only on the vaccine but also on the proportion of the population vaccinated. Hence, we would not expect the relative risk observed in different populations to be alike unless they had similar vaccine coverage. It is not enough to consider the uptake in the target population, as the coverage of the population studied also needs to be taken into account. If vaccination is only offered to 12–13-year-olds, there will be no observed effect in 15–19-year-olds within 2 years of vaccination.

A simple correction could be used to estimate the effect of vaccination in vaccinated individuals (assuming that the underlying risk in vaccinated and unvaccinated individuals was the same and ignoring herd immunity). If we suppose the observed relative risk of disease (post-vaccination relative to pre-vaccination) is R and the vaccination coverage is C in the cohort under study, then a crude estimate of the efficacy (E) would be $E = \min(1, 1 - [R - (1 - C)]/C)$, [A: we have edited this to house style, please check for accuracy] with the minimum imposed to prevent having greater than 100% efficacy. Meta-analysis of this quantity would provide a more easily interpretable effect measure. We hypothesise that the enormous heterogeneity reported for measures of efficacy would be greatly reduced by transforming to an efficacy scale.

We applied this transformation to data provided in the Article's appendix (p 47, figure S1A) for ~~changes in~~ the prevalence of HPV infections—girls aged 13–19 years. **[A: please check OK as edited and confirm page number is correct]** We were unable to reproduce Drolet and colleagues' results precisely, but (before transformation) obtained an I^2 of 95% for 1–4 years **[A: of follow-up?]**, 71% for 5–8 years, and 93% overall, and the heterogeneities were highly significant. Adjusting for vaccine coverage, the I^2 values were 42% for 1–4 years, 0% for 5–8 years, and 33% overall, and none were significant. Further, the pooled vaccine efficacy was ~~92~~% for 1–4 years, ~~99~~% **[A: Please provide these percentages to 1 decimal place for consistency]** for 5–8 years, and 97·6% overall (with 95% CI of ~~at least~~ 94·8%).**[A: Please provide the confidence interval as a range. Or do you mean the upper 95% confidence limit was at least 94·8%?]**

These data show that **[A: OK to add?]** the impact of HPV vaccination on HPV type 16 ~~or~~ 18 **[A: correct?]** infections in girls has been substantial. After adjusting for vaccine coverage, vaccine efficacy is both homogeneous across populations and remarkable **[A: remarkably high?]**.

[A: could you please add a statement about conflict of interests? (eg, "we declare no competing interests", or "PS declares…")]

Peter Sasieni, Jack Cuzick
peter.sasieni@kcl.ac.uk

Clinical Trial Units, King's College London, London SE1 9RT, UK (PS); and Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK (JC)

1   Drolet M, Bénard É, Pérez N. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; **394**: 497–509.