JOURNAL REVIEW

Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study

Romanowski B, Schwarz TF, Ferguson LM, *et al. Hum Vaccin* 2012;**7**:1374–1386.

Good news – it would appear that two doses of the bivalent human papillomavirus (HPV) vaccine elicit "non-inferior" levels of antibodies in young women compared to three doses. Romanowski *et al.* compared the licensed formulation/schedule of three doses of 20 µg antigen per dose at 0, 1 and 6 months with three two-dose strategies: (1) two doses of 20 µg at months 0 and 6, (2) two doses of 40 µg at months 0 and 6 and (3) two doses of 40 µg at months 0 and 2. Performance of the strategies was measured by quantifying geometric mean antibody titre 1 month after the final dose and at 24 months, with responses stratified by age band (9–14, 15–20 and 20–25 years). A key measure of success was the comparison of antibody levels elicited in the 9–14-year-olds (the target population for most immunisation programmes) with those levels in young women (aged 15–25 years) in whom clinical efficacy had been demonstrated through previous studies.

Strategy 3 (40 µg/dose at months 0 and 2) induced the lowest antibody levels and was classed as inferior in two of the age categories 1 month after final dose and in all ages at 24 months. Crucially, two doses of the standard (20 µg) formulation at 0 and 6 months in 9–14-year-olds generated antibody levels that were non-inferior to young women aged 15–25 years.

Given the amount of sub-analysis in the article (different schedules, antigen concentration and age) the data are presented clearly. However, there are caveats to consider before deciding on how this knowledge can be applied. This is ostensibly an immunological, laboratory study; virological and clinical endpoints were not assessed thus clinical efficacy is implied rather than demonstrated. It was also a relatively small study (960 subjects in total) with disaggregation of the data into age groups clearly having an impact on the power of associated observations. In addition, only 3% of recruits were of non-Caucasian European ethnic heritage. Lastly, as the authors admit, we still do not know what a definitive "safe" antibody level is (i.e. the elusive correlate of protection).

Caveats aside, it would be churlish to ignore these encouraging if somewhat preliminary observations, particularly as similar (positive) findings have been associated with two doses of the quadrivalent vaccine.[1] Having a two- rather than three-dose strategy has obvious cost and logistical benefits. Data on HPV immunisation coverage in countries with national programmes have shown waning compliance associated with dose number, particularly in older "catch-up" populations. A recent article that focused on the Australian catch-up population (aged 18–26 years) estimated coverage at 55.2% for dose 1, 44.8% for dose 2 and 31.7% for dose 3.[2] Another key aspect of these data is the importance of schedule: in terms of antibody response the schedule at 0 and 6 months (standard formulation) outperformed the one at 0 and 2 months, even when the latter contained twice the antigen content. This observation would suggest that those studies where vaccine impact is examined or predicted in women who have not completed three doses should take into account not simply the number of doses but when they were administered.

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2 **Brotherton J**, Gertig D, Chappell G, *et al*. Catching up with the catch-up: HPV vaccination coverage data for Australian women aged 18–26 years from the National HPV Vaccination Program Register. *Commun Dis Intell* 2011;**35**:197–201.

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