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Comment and Reply
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Commentary on opinion pieces re Australian human papillomavirus vaccine policy

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With respect to vaccination programs against human papillomavirus (HPV), Australia is unique in several respects. First, the scientific breakthrough of making virus-like particles (VLPs), the technology underpinning all current HPV vaccines, was made in Australia by Fraser and Zhou.[1] Second, although comparable bodies to review the cost-effectiveness of drugs exist in other countries, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia is the only such group responsible for assessment of the cost-effectiveness of vaccines.[2] Third, Australia was the first country to mount a fully-funded HPV immunisation program for all females aged 12 to 26 years. This program used a quadrivalent HPV vaccine including VLPs for types 6, 11, 16 and 18 manufactured by Merck and Co (Gardasil®, New Jersey, USA). Although other countries have since funded national programs, the Australian catch-up program, which came to an end in December 2009, remains the broadest in scope. As high coverage was achieved rapidly in the school-based cohort[3] and, based on more limited data, also in the catch-up cohort over 18 years of age,[4] Australia also has a unique opportunity for early evaluation of this comprehensive program. Now that a second, bivalent, vaccine Cervarix® (GSK, Uxbridge, UK) has been judged cost-effective for use in the National Immunisation Program by the PBAC, what are the implications for future HPV vaccine use in Australia?

The commentaries by Stern[5] and Wain[6] have reviewed the complex evidence base for the quadrivalent and bivalent HPV vaccines in some detail but come to somewhat different conclusions. Two facts are not in dispute – both vaccines are highly effective in preventing infection due to HPV 16 and 18, and that only the quadrivalent vaccine is effective against HPV types 6 and 11. Two important questions remain. The first, not addressed by either commentary, is the aim of the HPV program. Is the aim limited to prevention of cancer and other conditions with long-term impact on quality of life, or is it a broader one of preventing any HPV-related morbidity? The second question, which the two commentaries answer with different degrees of uncertainty, is does the bivalent vaccine afford superior protection against HPV 16 and 18, particularly in the long-term?

If the aim of HPV vaccination is only to prevent severe and long-term morbidity, then with respect to HPV 6 or 11 infection, it is arguable that this applies only to recurrent respiratory papillomatosis (RRP). RRP is a potentially life-threatening condition causing recurrent airway compromise due to warty growths, due to intrapartum acquisition of HPV types 6 and/or 11. It is rare (incidence ~3 per 100 000 children) and usually presents at 3 to 4 years.[7] If protection against infection due to types 6 and 11 persists for long enough after receipt of quadrivalent vaccine by the mother, this condition could be greatly reduced or eliminated. If the aim of the program is broader, then data from Australia and elsewhere suggest substantial short-term morbidity from genital warts in the second or third decade of life.[4] Reduction in genital warts has the advantage of ease of measurement and a short time frame, with vaccine impact reported from an Australian sexual health clinic little more than 12 months after the program commenced.[4] A detailed economic analysis using UK data estimated the quality-adjusted life-years (QALY) gained from prevention of genital warts to be ~10% of the total, assuming an average duration of vaccine protection of 20 years.[8]

Could lack of genital wart protection be counter-balanced by superior protection (due to either or both of greater protection against related types and increased duration of immunity) against the oncogenic types, 16 and 18? With respect to protection against oncogenic types, a crucial factor in overall cost-effectiveness of HPV vaccine is the flow-on impacts on the cervical screening program. An analysis from the Netherlands concluded that, given the performance of that country's cervical screening program, HPV vaccine would not be cost-effective without substantial reductions in the cost of vaccine.[9] In the UK, the single most important variable in overall cost-effectiveness of HPV vaccination was the duration of immunity. The cost effectiveness ratio almost doubled from $US30 000 per QALY, if there was life-long immunity, to almost $US70 000 if immunity only lasts 10 years.[8]

The importance of duration of immunity makes this a significant consideration in comparing the bivalent and quadrivalent vaccines. Such comparisons are difficult, as long-term data on clinical outcomes are limited, which inevitably means that interpretation of immunological correlates of protection is also limited. Given the different designs of the clinical trials for each vaccine, there is abundant scope for manufacturers to argue that outcome data, including surrogate immunological markers, cannot be validly compared. One commentary presents credible, but inconclusive, data for both similar clinical trial endpoints and independent measures of comparative antibody response as measures of protection against HPV 16 and 18, both of which favour the

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bivalent vaccine.[5] The other commentary asserts that the higher antibody responses at 12 months against types 16 and 18 in the comparative immunogenicity trial are not clinically relevant and points to a higher level of local reactions for bivalent vaccine.[6]

Should Australia use only bivalent or only quadrivalent HPV vaccine?

In my view, the information presented in the commentaries leave vaccine choice in equipoise, for the primary aim of HPV vaccination, the prevention of HPV-related cancer. While it is undeniable that only quadrivalent HPV vaccine provides protection against genital warts, the currently available evidence for oncogenic types favours longer duration of immunity for bivalent vaccine. If this means that no or less boosting is required, which can only be determined from clinical outcomes, this is likely to be more important for cost-effectiveness than lack of wart protection. Over time, this issue will become irrelevant, as higher valency vaccines will include a wider, and probably common, range of HPV types. In the meantime, the other issues which always beset those administering vaccines in the field and policy makers, but which manufacturers have no incentive to address, those relating to the necessary number of doses and mixed schedules, remain. The possibility that two doses of quadrivalent vaccine given to girls under the age of 12 years might give more robust antibody responses than seen following three doses in older females is being evaluated.[10] If so, the next logical step would be evaluation of mixed schedules. Two doses of quadrivalent vaccine, followed by a third dose of bivalent vaccine, might provide the optimum blend of broadest protection and greatest duration of immunity. At the very least, information about responses to mixed schedules would make managing travel between jurisdictions and the management of putative adverse events more straightforward, but we will have to rely on enterprising independent researchers to investigate such possibilities.

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