

## “I want the one for older women” — extending the human papillomavirus vaccine population base

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*Cervical cancer prevention relies on two different age-specific technologies, and consumers should not be misled about the role of HPV vaccines*

The introduction of human papillomavirus (HPV) vaccines to clinical practice is the end result of a remarkable distillation of basic science, new technology, epidemiological understanding, clinical research and commercial development. It has brought together stakeholders from a variety of backgrounds to consider these developments, and Australia is now the first country to implement a population-based mass vaccination program against HPV. The Australian HPV vaccination program was commenced after cost-effectiveness of the quadrivalent vaccine was demonstrated,<sup>1</sup> anticipating that the expected reduction in the cost of treating HPV-related disease in Australian women would compensate for the cost of the vaccine. This program, an Australian Government initiative,<sup>2</sup> appears to have been very successful in terms of coverage, and offers young Australian women the opportunity to be among the first national cohort to be vaccinated against the virus types that cause most cervical cancers and a variety of other HPV-related diseases.

The natural history of HPV infection and the consequent risk of developing cervical cancer are well documented. HPV infection, replication and particle maturation occurs in the stratified squamous epithelia of skin and mucous membranes, with virus spread occurring by skin-to-skin contact. Most people encounter genital HPV soon after the onset of sexual activity,<sup>3</sup> with the highest risk of contracting the infection in the first 5–10 years after commencing sexual activity. The clinical consequences of infection will vary according to the type of HPV encountered, and most infections resolve spontaneously, presumably relying on the host's immune system to clear the infection. For whatever reason, some individuals do not clear their infections, and if these infections are caused

by some oncogenic or high-risk varieties of HPV, this persistence will lead to activation of oncogenic viral proteins, the loss of cellular control mechanisms and the potential for malignant transformation. Screening programs based on cytology have had significant impacts on the incidence and mortality of cervical cancer by detecting these potential cancer precursors, but HPV vaccines allow the opportunity to enlist the vaccinee's own immune system to develop neutralising antibodies before exposure, and to primarily prevent the infection.

The two currently available vaccines (a quadrivalent vaccine against HPV types 6, 11, 16 and 18, and a bivalent vaccine against types 16 and 18) have both been developed by recombinant genetic technology that allows expression of the major structural protein of HPV, the L1 protein, that spontaneously assembles into virus-like particles (VLPs) which are both type-specific and highly immunogenic. Both available vaccines contain VLPs, but the products differ in the types of HPV L1 proteins included as antigens, substrates used for production, adjuvant properties and in the final formulation. Antibodies raised to the VLPs provide protection against HPV infection, probably by transudation of IgG from serum to local mucosal/epithelial areas, especially at sites of trauma where HPV can otherwise gain access to basal epithelial cells.<sup>4</sup> Published efficacy studies suggest subtle but probably insignificant differences between the two vaccines in preventing type-specific HPV infections and disease.<sup>5,6</sup> It seems unlikely that cell-mediated immunity is involved as a direct effector mechanism of vaccine protection.<sup>7</sup>

Clearly, this mode of action highlights that the current vaccines will only be effective if administered before exposure. These

vaccines have shown no therapeutic efficacy for pre-existing infections.<sup>8</sup> Trials of both commercially available vaccines, while demonstrating very high efficacy (approaching 100%) in HPV-naïve populations, have shown diminished efficacy in populations with high rates of previous exposure.<sup>4,5</sup> The results so far have indicated that women already infected with one of HPV types 16 or 18 can be protected against development of cervical intraepithelial neoplasia grade 2/3 or cervical adenocarcinoma in situ associated with the other type by vaccination. Both trials were conducted in young populations (generally in women aged between 16 and 25 years). Preliminary results indicating significant efficacy (greater than 90%) of the quadrivalent vaccine in an older population aged between 24 and 45 years have been presented, and these data form the basis of the vaccine sponsor's application to regulatory authorities in both Australia and the United States for expansion of their age indication for this formulation.<sup>9</sup>

Doctors are used to being exposed to marketing from drug companies, and are susceptible to commercial persuasion with competing claims of superiority and product distinction. The quadrivalent vaccine, Gardasil (Merck), is available at no cost to Australian girls and women between the ages of 12 and 26 as part of the National Immunisation Program. The bivalent vaccine, Cervarix (GlaxoSmithKline), has to date not been included in the program, having initially been rejected by the Pharmaceutical Benefits Advisory Committee (PBAC) on the basis of uncertain cost-effectiveness,<sup>10</sup> but subsequently recommended for inclusion.<sup>11</sup> This recommendation has not yet been endorsed by the Australian Government. The sponsoring company appears to have decided to promote Cervarix specifically to older women,<sup>12</sup> despite the absence of efficacy data and the uncertain population benefits in this age group.

Indeed, the decision by the Australian Therapeutic Goods Administration (TGA) to register Cervarix for use in this population, in which no efficacy has been shown, is not easily understood. Under the *Therapeutic Goods Act 1989* (Cwlth), the TGA is responsible for evaluating the quality, safety and efficacy of medicines.<sup>13</sup> The World Health Organization has issued guidelines for the evaluation of HPV vaccines, indicating that studies that use immunogenicity data to bridge efficacy from younger to older women are not appropriate.<sup>14</sup> In Australia, these guidelines have not been adhered to, and Cervarix has been licensed for use in women up to 45 years of age, despite lack of demonstrated efficacy in women over 26 years. To suggest that the vaccine will offer patients some theoretical potential benefit if they are prepared to pay for it does not reflect sound evidence-based, equitable health care provision.

The promotion and media coverage of HPV vaccines in Australia have been extensive, and with this has come an increased awareness of HPV, its relation to cervical cancer, and the national HPV vaccination program. The promise of a cancer vaccine is alluring to women who perceive a risk of cervical cancer. Principles of consumer protection, however, demand that expectations should not be raised unduly, and that the available vaccine does not promise to deliver beyond its capacity. Excessive promotion in the older age group, when the vaccine is likely to be of substantially reduced efficacy because of either previous exposure or reduced risk of future exposure, potentially diverts attention and compliance with established methods of cervical cancer prevention based on cervical cytology.

HPV vaccines are about preventing future infections. Cervical cytology detects cytological abnormalities from previous infections. It is important that the benefits of these two approaches to cervical cancer prevention are not confused, and that all women receive the best and most appropriate combination of two effective technologies.

### Competing interests

I am the Chair of the CSL Gardasil Advisory Board. I have received speaker fees, travel assistance and consultancy fees from CSL Biotherapies and from Merck and its affiliates in relation to Gardasil. I hold shares in CSL Limited.

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