

Systematic Review of the Safety, Immunogenicity and Efficacy of Human Papillomavirus Vaccines March, 2007

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1 Background

This review underpins the recommendations on the use of human papillomavirus vaccines in Australia as made by the Australian Technical Advisory Group on Immunisation (ATAGI), and endorsed by the NHMRC, in the 9th edition of *The Australian Immunisation Handbook*. This review should be read in conjunction with sections of the 9th edition of *The Australian Immunisation Handbook*: Chapter 3.7 Human papillomavirus and Appendix 2 *Handbook* development (available online at <http://immunise.health.gov.au/>).

2 Aim

The aim of this review is to assist in the development of recommendations for the use of human papillomavirus vaccines in Australia.

3 Methods

The following methods were used in this systematic review, according to NHMRC requirements.¹⁻³ The review was based on the following overall structured research question:

In humans (females and males), is intramuscular immunisation (vaccination) with virus-like particle based human papillomavirus vaccines immunogenic, safe and effective in preventing persistent human papillomavirus infection and related cervical and genital lesions?

3.1 Systematic identification and review of the scientific literature

3.1.1 Search strategy: databases and period searched

The following databases were searched to identify randomised controlled trials relevant to the review questions: The Cochrane Library (comprising the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, and the NHS Economic Evaluation Database) as at 17.9.2006; MEDLINE Daily Update (from 1966 to 17.09.06) and EMBASE (from 1980 to Week 37, 2006) as at 17.9.2006.

To minimise the introduction of bias, no limits with respect to date, language or abstract were used. Searches were limited to randomised controlled trials. Search strategies varied slightly between databases depending on the availability of

controlled vocabulary (thesaurus) terms and/or limits. A combination of thesaurus terms and truncated free text terms were utilised to maximise retrieval. The search terms and search strategies used are available in **Appendix C**.

3.1.2 Additional search methods

Additional search methods included interaction with expert sources, from the United States Centers for Disease Control and Prevention (CDC), checking and retrieval of studies in reference lists of identified clinical trials and review papers, and hand searching (relevant conference abstracts, and other sources).

Additional data supplied to ATAGI included commercial-in-confidence dossiers from the pharmaceutical companies, CSL Biotherapies/Merck & Co Inc and GSK, respectively, summarising unpublished data relevant to the licensure of the respective human papillomavirus vaccines, the quadrivalent vaccine Gardasil and the bivalent vaccine Cervarix, examined in this review. However, unpublished data that remains commercial-in-confidence have not been included in this review.

3.1.3 Inclusion and exclusion criteria

The inclusion criteria were based on the study question as follows:

Population/problem:	Females and males (all ages) at risk of HPV infection
Intervention:	Parenteral administration of virus-like particle (VLP) based vaccines
Comparator:	No immunisation (in healthy subjects) OR Placebo immunisation (in healthy subjects)
Outcomes:	Immunogenicity (antibody or other, eg. B/T cell, responses) Various measures of efficacy and safety (see below)
Study design:	Randomised controlled trials or systematic reviews
Languages :	Any

The following specific exclusion criteria were applied:

- other HPV vaccines/other vaccines (eg. therapeutic vaccines that are not VLP based, rubella vaccine called HPV-77)
- animal studies
- study data provided as ‘commercial-in-confidence’
- review articles with no original data.

3.2 Questions specifically addressed in this systematic review

The following outcomes regarding human papillomavirus vaccine, immunogenicity, efficacy and safety in humans were reviewed:

For each component of the review (immunogenicity, efficacy and safety), data was specifically considered for the following groups:

- a) Females aged 10 to 13 years
- b) Females aged 14 to 18 years
- c) Females aged 19 to 26 years
- d) Males

3.2.1 Immunogenicity of human papillomavirus vaccination

The following measures of immunogenicity were extracted into the primary data extraction tables:

- a) Type specific HPV antibody responses in sera
- b) Neutralisation of HPV by vaccine induced antibodies
- c) Cytokine responses
- d) Lymphoproliferative response
- e) Type specific HPV antibody responses in cervicovaginal lavage specimens
- f) Other

Summary **Table 4** only includes tabulated data for the primary outcome of type specific HPV antibody responses in sera, as this was the most consistently used and concise summary measure of an immune response to HPV vaccine.

3.2.2 Efficacy of human papillomavirus vaccination

The following outcomes were reviewed:

- a) persistent genital HPV infection (cervical/other) with (i) all HPV types or (ii) HPV types covered by the vaccine
- b) low grade cervical dysplasia associated with HPV infection with (i) all HPV types or (ii) HPV types covered by the vaccine
- c) high grade cervical dysplasia associated with HPV infection with (i) all HPV types or (ii) HPV types covered by the vaccine
- d) vaginal/vulval dysplasia associated with HPV infection with (i) all HPV types or (ii) HPV types covered by the vaccine
- e) genital warts associated with HPV infection with (i) all HPV types or (ii) HPV types covered by the vaccine

The measure of effect used was vaccine efficacy, which is calculated as 1 minus relative risk.

3.2.3 Safety profile of human papillomavirus vaccination

The following adverse events were reviewed:

- a) Local reactions at the injection site
- b) Systemic reactions – fever, headache, malaise, fatigue, gastrointestinal symptoms, rash
- c) Serious adverse events, eg. hospitalisation
- d) Death
- e) Other adverse events

3.3 Questions which were not systematically reviewed

The cost-effectiveness of human papillomavirus vaccines has not been reviewed, as the purpose of this review was to review safety, immunogenicity and efficacy. Appraisal of the cost-effectiveness of vaccines is outside the mandate of the Australian Technical Advisory Group on Immunisation and is assessed by the Pharmaceutical Benefits Advisory Committee.

In addition to the information presented in this systematic review, ATAGI reviewed the best available evidence on the clinical disease and epidemiology of human papillomavirus disease in Australia, including the prevalence of type specific human

papillomavirus infection and disease. This and other information is presented in the 9th edition of *The Australian Immunisation Handbook*, Chapter 3.7 Human papillomavirus (**Appendix A**) and contributed to the development of recommendations on the use of human papillomavirus vaccines.

3.4 Appraisal of included studies

The appraisal of studies included in the review was performed as set out in the NHMRC toolkit publication “How to review the evidence: systematic identification and review of the scientific literature”.¹ Data from each randomised controlled study included in the review was extracted into a standardised data extraction form (see **Appendix B**) and assessed using the critical appraisal checklist and descriptive comparisons as described in the NHMRC handbook “How to review the evidence: systematic identification and review of the scientific literature”. The quality appraisal tables, together with level of evidence and grading of the body of evidence tables, are shown in **Appendix B**.¹⁻³

3.5 Assessment and application of scientific evidence

Application of NHMRC dimensions of evidence of clinical importance and relevance were made to all primary outcomes in included studies (including NHMRC levels of evidence and a quality assessment) as set out in the NHMRC toolkit publication “How to use the evidence: assessment and application of scientific evidence” – Section 1.² (see also **Appendix B**).

3.6 Assessment of the body of scientific evidence

Assessment of the body of scientific evidence was performed using a considered judgment form, as described by the NHMRC pilot program (<http://www.nhmrc.gov.au/consult/index.htm>)³ (see **Appendix B**).

4 Results

4.1 Search results and studies identified

There were 483 records retrieved by the database searches (Embase n=226, Medline n=200, Cochrane Library Central Register of Controlled Trials n=47, Cochrane Library NHS Economic Evaluation Database n=7, Cochrane Library Database of Systematic Reviews n=2, Cochrane Library Health Technology Assessment Database n=1). All available abstracts (some records from the 1960s had no abstracts) were independently reviewed by two study authors. Following the removal of duplicates and the application of inclusion and exclusion criteria, relevant and possibly relevant studies were retrieved and reviewed for inclusion (n=23). Of these, 17 studies were identified for inclusion in the review and are listed in **Table 1**. Of these, 16 contained information about immunogenicity, 10 about safety and 6 about efficacy. Six studies were excluded from the review for the reasons stated in **Table 2**.

4.2 Appraisal of included studies

Table 3 provides a summary of the study design and quality assessment for each of the included studies.

4.3 Assessment and application of scientific evidence

Assessment of the applicability of the evidence is presented in **Table 4**, for the clinical questions regarding vaccine immunogenicity, in **Tables 5a-e** for the clinical questions regarding vaccine efficacy and **Tables 6a-e** for the clinical questions regarding vaccine safety. Where possible, grading of both the clinical importance and relevance has been included.

4.4 Assessment of the body of evidence

Assessment of the body of evidence, as presented in **Tables 7, 8 and 9**, refers to the routine use of human papillomavirus vaccines in Australia (**Appendix A**).

As described in **Table 3**, there were no efficacy studies of human papillomavirus vaccines in males. The studies included in this systematic review contained very limited data regarding the immunogenicity and safety of human papillomavirus vaccines in males, with two Phase I studies including male subjects.^{4,5} The grading for the immunogenicity and safety of human papillomavirus vaccine in males has been based on additional data provided as commercial-in-confidence, some of which is now publicly available⁶⁻⁸ or presented in the product information (PI) for the quadrivalent vaccine Gardasil.

As described in **Table 3**, there were no efficacy studies of human papillomavirus vaccines in females aged 10–14 years. This is due to the ethical difficulties with the collection of genital specimens in pre-adolescent females. In the absence of clinical efficacy data, the recommendation for the use of human papillomavirus vaccines in females aged 10–13 years has been based on bridging immunogenicity and safety data and expert opinion.

No published immunogenicity or safety studies of girls aged 10–14 years were identified in the body of this review. The grading for the immunogenicity and safety of human papillomavirus vaccine in females aged 10–13 years has been based on additional data provided as commercial-in-confidence, some of which is now publicly available⁶⁻⁸ or presented in the product information (PI) for the quadrivalent vaccine Gardasil.

4.5 The link between the evidence and recommendations in the 9th edition of *The Australian Immunisation Handbook*

The guideline recommendations are shown in Chapter 3.7 Human papillomavirus of the 9th edition of *The Australian Immunisation Handbook* (see **Appendix A** of this review). The link between the evidence reviewed here and the *Handbook* chapter is stated by reference to this review throughout the chapter and through use of the NHMRC grades of recommendation after each recommendation regarding use of the vaccine.

5 References

1. National Health and Medical Research Council (NHMRC). How to review the evidence: systematic identification and review of the scientific literature. Canberra: NHMRC, 1999.

2. National Health and Medical Research Council (NHMRC). How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC, 2000.
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7. European Medicines Agency. EPARs for authorised medicinal products for human use. Gardasil. Available at: <http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm> (accessed Feb 2007).
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