Table 7: NHMRC - Assessing the body of evidence for HPV immunogenicity

Key question: Are VLP based HPV vaccines immunogenic in humans? *(Circle appropriate grade for each component)*		Evidence table ref: Brown 2001 Evans 2001 Harro 2001 Koutsky 2002 Emeny 2002 Pinto 2003 Ault 2004 Fife 2004 Harper 2004 Pinto 2005 Poland 2005 Villa 2005 Harper 2006 Villa 2006 Giannini 2006 Mao 2006
1. Volume of evidence *(quantity, level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)*		
A: Several level II studies of high methodological quality and relevance to women aged 16–26 years (and some up to age 45, eg. Evans 2001, Harro 2001, Giannini 2006), with low risk of study bias. Although most (but not all) studies were sponsored by the vaccine developers, the quality and consistency of studies indicated a low risk of study bias. Only two Phase I studies (level II evidence but of limited sample size) (Harro 2001, Evans 2001) included males aged 18–45 years in whom the vaccine was immunogenic.	(A)	**Excellent** (several level I or II studies with low risk of bias)
	B	**Good** (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)
	C	**Satisfactory** (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)
	D	**Poor** (Level IV studies or Level I to III studies with high risk of bias)
2. Consistency *(the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group formed a judgement as to the overall direction of the evidence)*		
A: Several level II studies consistently demonstrated the immunogenicity of human papillomavirus vaccines.	(A)	**Excellent** (all studies consistent)

There were no conflicting results. This is despite there being no standard methodology for measuring HPV antibody responses.		
	B	**Good** (most studies consistent and inconsistency can be explained)
	C	**Satisfactory** (some inconsistency, reflecting genuine uncertainty around question)
	D	**Poor** (evidence is inconsistent)
3. **Clinical impact** *(the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)*		
	A	**Excellent** (very large clinical impact)
B: HPV vaccines will have a substantial clinical impact in sexually active women by averting HPV related cervical dysplasia due to HPV16 and HPV18 and, in the case of the quadrivalent vaccine, genital warts. There will be a continuing need for Pap screening programs due to the occurrence of disease due to HPV types not covered by the vaccines. The potential clinical impact will be largest in women who have not yet been exposed to/infected with HPV. This is women prior to first sexual activity and the most feasible proxy for this status is age. Thus the largest clinical impact will be in women aged 10–13 years, although the disease burden prevented through vaccination will not be achieved in this cohort until they become sexually active. Vaccination of women aged 14–18 and 19–26 years will prevent disease sooner, although the overall clinical impact in terms of disease reduction within those age cohorts will be lower than that achievable in the youngest cohort as some women will already be infected with HPV types covered by the vaccine. Duration of immunity is at least 5 years but requires ongoing monitoring in order to implement booster vaccination if needed. The potential clinical impact in males is not known due to an absence of efficacy data in males.	(B)	**Good** (substantial clinical impact)
	C	**Satisfactory** (moderate clinical impact)
	D	**Poor** (slight or restricted clinical impact)
4. **Generalisability** *(how reasonable is it to generalise from the results of the studies used as evidence to the target population for this guideline?)*		
	A	**Excellent** (directly generalisable to target population)
B: Populations studied are similar to the Australian female target population. Australian subjects participated in one trial. However, exclusion criteria for trials included women with 4 or more sexual partners and a past history of Pap test abnormalities or genital warts. Median number of lifetime sexual partners in Australian women varies by age: 2.0 for women aged 16–19 and over 4 for women aged 20–49. Therefore, many Australian women have a higher probability of prior HPV infection with vaccine types than women in the trials, and therefore, vaccine effectiveness in the population can be expected to be lower than the efficacy	(B)	**Good** (directly generalisable to target population with some caveats)

achieved in the trials. There is evidence that women already exposed to HPV produce a higher titre antibody response following vaccination. However, it is unclear whether women who have previously cleared an HPV infection with a vaccine type remain at any substantial risk of subsequent reinfection and disease due to that type. Women with an exisiting HPV infection do not benefit from vaccination against that type (ie. vaccination does not assist clearance or prevent disease related to persistent infection with that type).		
	C	Satisfactory (not directly generalisable to the target population but could be sensibly applied)
	D	Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply)
5. Applicability *(the extent to which the body of evidence is directly applicable to Australian healthcare context)*		
	A	Excellent (directly applicable to Australian healthcare context)
B: Highly applicable particularly given the high levels of participation in the National cervical screening program, although the program recommends less frequent screening than conducted in the trials. There are no routinely available means of screening women pre-vaccination for past or current type specific HPV infection.	(B)	Good (applicable to Australian healthcare context with few caveats)
	C	Satisfactory (probably applicable to Australian healthcare context with some caveats)
	D	Poor (not applicable to Australian healthcare context)

6. Other factors *Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)* Larger vaccine trial databases continuously updated with all trial participants' details are held by the vaccine manufacturers. Current data (as at the time of submission of the vaccines for review) was made available and also supported the immunogenicity of HPV vaccines in humans. Data similar to that reviewed is now publicly available for the quadrivalent vaccine at the FDA website (U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting May 18, 2006. Briefing information. 2006. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm (accessed Jun 2006)), at the European Medicines Agency website (http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm (accessed Feb 2007)) and from Canadian NACI HPV Vaccine recommendations (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf (accessed March 2007)). No published studies of girls aged 10–15 years were identified in the body of this review but unpublished trial data, presented as commercial-in-confidence, and now publicly available (see Gardasil product information and references above), indicates at least equivalent immunogenicity to	

that observed in women aged 16–26 years. This data resulted in the upgrading of the immunogenicity recommendation in females aged 10–13 years. Unpublished trial data, presented as commercial-in-confidence, and now publicly available (see Gardasil product information and references above), indicates at least equivalent immunogenicity in males aged 9–15 years as that observed in women aged 16–26 years. This data resulted in the upgrading of the immunogenicity recommendation in males.			
EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*			
The volume, consistency, clinical impact, generalisability and applicability of the body of evidence regarding the immunogenicity of human papillomavirus vaccines in humans are considered very good to excellent. When given as a 3-dose series, HPV vaccines elicit antibody titres many times higher than those observed following natural infection. Antibody responses peak at month 7 (1 month after dose 3) at between 7 and 150 times that seen following natural infection, depending upon the HPV type, and appear to plateau at 18 to 24 months. It should be noted that there is no standard serological assay for detecting HPV antibodies and no protective titre has been established. Overall, seroconversion occurs in 99 to 100% of those vaccinated. The duration of immunity from vaccination is not yet known (but is of at least 5 years duration); hence, it is possible that booster doses may be required in the future. Quadrivalent HPV vaccine has been administered concomitantly with hepatitis B vaccine in clinical trials, with no reduction in immunogenicity of either vaccine observed. There are no clinical data regarding concomitant administration of the quadrivalent HPV vaccine with adolescent/adult formulation dTpa or varicella vaccine, but there is no reason to anticipate any adverse outcomes if they are given simultaneously.	Component	Descriptor	Grade
	Volume of evidence	Excellent	A
	Consistency	Excellent	A
	Clinical impact	Good	B
	Generalisability	Good	B
	Applicability	Good	B
RECOMMENDATION *What recommendation (s) does the guideline development group draw from this evidence?*		The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B.	

(i) Females aged 10 to 13 years HPV vaccine is recommended for females 10 to 13 years of age.	IMMUNOGENICITY B
(ii) Females aged 14 to 18 years HPV vaccine is also recommended for all females 14 to 18 years of age. Whilst some females in this age group will already have commenced sexual activity, the majority will not yet be infected with a HPV vaccine type.	A
(iii) Females aged 19 to 26 HPV vaccine is also recommended for all females 19 to 26 years of age.	A
(iv) Females aged 27 years and over Quadrivalent HPV vaccine is not registered for use in females over the age of 27 years as there are no safety or efficacy data to support its use in this age group.	bivalent vaccine – B quadrivalent vaccine – no data
(v) Males Although quadrivalent HPV vaccine is licensed for use in males aged 9 to 15 years, vaccination of males is not recommended at this time due to the lack of clinical efficacy data. Although HPV vaccine produces high antibody titres in males, it is not known whether vaccination of males can either prevent transmission of HPV or provide protection against genital HPV infection, genital warts, anogenital dysplasia or anogenital cancers.	age 9–15 – B other ages – no data
	Grade of recommendation see above

Table 8: NHMRC - Assessing the body of evidence for HPV efficacy

Key question: Are VLP based HPV vaccines efficacious in preventing type specific HPV infection/cervical disease/external genital lesions? *(Circle appropriate grade for each component)*		Evidence table ref: Koutsky 2002 Brown 2004 Harper 2004 Villa 2005 Harper 2006 Mao 2006
1. Volume of evidence *(quantity, level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)*		
A: Several level II studies of high methodological quality and relevance to women aged 15–26 years with low risk of study bias. Although studies were sponsored by the vaccine developers, the quality and consistency of studies indicated a low risk of study bias. There is no efficacy data in males or in females aged 10–14 years.	(A)	Excellent (several level I or II studies with low risk of bias)
	B	Good (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)
	C	Satisfactory (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)
	D	Poor (Level IV studies or Level I to III studies with high risk of bias)
2. Consistency *(the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group formed a judgement as to the overall direction of the evidence)*		
A: Several level II studies consistently demonstrated efficacy of human papillomavirus vaccines in preventing type specific genital infection, genital warts and cervical disease in women aged 15–26 years. There were no conflicting results regarding clinical efficacy outcome measure.	(A)	Excellent (all studies consistent)
	B	Good (most studies consistent and inconsistency can be explained)
	C	Satisfactory (some inconsistency, reflecting genuine uncertainty around question)
	D	Poor (evidence is inconsistent)
3. Clinical impact *(the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the*		

question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)		
	A	**Excellent** (very large clinical impact)
B: The anticipated clinical impact of the recommendation is substantial. Consistently demonstrated vaccine efficacy is essential as a basis of a recommendation for use of human papillomavirus vaccines in young Australian women as a preventative health measure. Pap testing has been highly successful in reducing cervical cancer but is invasive and treatment is potentially distressing. Vaccination should reduce the number of abnormal Pap tests and subsequent procedures. Vaccination will not replace the need for Pap testing. The potential clinical impact will be largest in women who have not yet been exposed to/infected with HPV. This is women prior to first sexual activity and the most feasible proxy for this status is age. Thus the largest clinical impact will be in women aged 10–13 years, although the disease burden prevented through vaccination will not be achieved in this cohort until they become sexually active. Vaccination of women aged 14–18 and 19–26 years will prevent disease sooner, although the overall clinical impact in terms of disease reduction within those age cohorts will be lower than that achievable in the youngest cohort as some women will already be infected with HPV types covered by the vaccine. Duration of immunity is at least 5 years but requires ongoing monitoring in order to implement booster vaccination if needed. The potential clinical impact in males is not known due to an absence of efficacy data in males.	B	**Good** (substantial clinical impact)
	C	**Satisfactory** (moderate clinical impact)
	D	**Poor** (slight or restricted clinical impact)
4. Generalisability *(how reasonable is it to generalise from the results of the studies used as evidence to the target population for this guideline?)*		
	A	**Excellent** (directly generalisable to target population)
B: Populations studied are similar to the Australian target population. Australian subjects participated in one trial. However, exclusion criteria for trials included women with 4 or more sexual partners and a past history of Pap test abnormalities or genital warts. Median number of lifetime sexual partners in Australian women varies by age: 2.0 for women aged 16–19 and over 4 for women aged 20–49. Therefore, many Australian women have a higher probability of prior HPV infection with vaccine types than women in the trials, and therefore, vaccine effectiveness in the population can be expected to be lower than the efficacy achieved in the trials. It is partricularly important to note that the highlighted efficacy outcomes of the published quadrivalent vaccine trials to date are in the 'According to Protocol' populations, ie. HPV naïve women who remain uninfected through to month 7 (ie. one month after last dose of vaccine). This population	B	**Good** (directly generalisable to target population with some caveats)

has been selected to highlight the maximum possible vaccine efficacy. This result could only be achieved in women who have not yet commenced sexual activity and who remain virgins through to completion of vaccination. Thus, the primary target population for HPV vaccine should be females who are not yet sexually active. Overall efficacy in women who are already sexually active is much lower.		
	C	**Satisfactory** (not directly generalisable to the target population but could be sensibly applied)
	D	**Poor** (not directly generalisable to target population and hard to judge whether it is sensible to apply)
5. **Applicability** *(the extent to which the body of evidence is directly applicable to Australian healthcare context)*		
	A	**Excellent** (directly applicable to Australian healthcare context)
B: Highly applicable particularly given the high levels of participation in the National cervical screening program, although the program recommends less frequent screening than conducted in the trials. There are no routinely available means of screening women pre-vaccination for past or current type specific HPV infection.	B	**Good** (applicable to Australian healthcare context with few caveats)
	C	**Satisfactory** (probably applicable to Australian healthcare context with some caveats)
	D	**Poor** (not applicable to Australian healthcare context)

6. Other factors *Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)* Larger vaccine trial databases continuously updated with all trial participants' details are held by the vaccine manufacturers. Current data (as at the time of submission of the vaccines for review) was made available and also supported the efficacy of HPV vaccines in humans, when given prior to HPV infection with targeted types. Data similar to that reviewed is now publicly available for the quadrivalent vaccine at the FDA website (U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting May 18, 2006. Briefing information. 2006. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm (accessed Jun 2006)), at the European Medicines Agency website (http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm (accessed Feb 2007)) and from Canadian NACI HPV Vaccine recommendations (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf (accessed March 2007)).	
EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the*	

above factors into account. Please indicate any dissenting opinions.			
The volume, consistency, clinical impact, generalisability and applicability of the body of evidence regarding the efficacy of human papillomavirus vaccines in females are considered very good to excellent. There is no efficacy data in males. It is important to note that HPV vaccines are prophylactic vaccines (ie. designed to prevent initial HPV infection). In women who are already infected with HPV types covered by the vaccines prior to vaccination (ie. HPV-DNA positive), the vaccines do not treat infection or prevent disease caused by that type. The optimal impact of HPV vaccine will be gained by vaccinating women who have not (yet) been infected with HPV (ie. pre-adolescent women, prior to sexual debut). In contrast, vaccine efficacy against HPV16/18-related CIN2/3 or worse in women who received at least 1 dose of quadrivalent vaccine, regardless of HPV status at the beginning of the trial(s), was 36.3% (95% CI: 19.4–49.9%).In this same population, the vaccine efficacy against high-grade CIN caused by any HPV type was 12.2% (95% CI: <0–25.3%). These data reflect the reduced impact of vaccinating women in whom a proportion will already have been infected with HPV (eg. older women who are non-virgins). In all women enrolled in quadrivalent HPV trials, the greatest benefit of vaccination was observed in those who were naïve to the relevant HPV vaccine types at the beginning of the trial(s) (HPV-DNA negative and seronegative), and who remained uninfected with these HPV types prior to completing the 3-dose vaccine schedule. In this group of women, the vaccine efficacy was 100% (95% CI: 93–100%) against HPV16/18-related CIN2/3 or worse. In addition, the efficacy of the quadrivalent vaccine against any HPV6/11/16/18-related CIN (of any grade) was 95% (95% CI: 87–99%) and against external genital lesions, including genital warts, was 99% (95% CI: 95–100%). The vaccine efficacy in this same population against high-grade CIN due to any HPV type, including non-vaccine types, was 16.9% (95% CI: <0–39.8%), indicating that a significant number of other HPV types cause cervical abnormalities against which the vaccine is not expected to be effective. If women who were HPV naïve at the beginning of the trial(s) but received fewer than 3 vaccine doses, or who became infected with a HPV vaccine type during the course of vaccination, were included in the analyses, then vaccine efficacy was still high: 99% against HPV16/18-related CIN2/3 or worse (95% CI: 93–100%), 94% against any HPV6/11/16/18-related CIN (of any grade) (95% CI: 88–97%), and 94% against external genital lesions, including genital warts (95% CI: 90–98%).	Component	Descriptor	Grade
	Volume of evidence	Excellent	A
	Consistency	Excellent	A
	Clinical impact	Good	B
	Generalisability	Good	B
	Applicability	Good	B
	The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of		

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence?* (i) Females aged 10 to 13 years HPV vaccine is recommended for females 10 to 13 years of age (on the basis of immunogenicity data demonstrating antibody responses of at least equal magnitude to those correlated with vaccine efficacy in older women and safety data). (ii) Females aged 14 to 18 years HPV vaccine is also recommended for all females 14 to 18 years of age. Whilst some females in this age group will already have commenced sexual activity, the majority will not yet be infected with a HPV vaccine type. (iii) Females aged 19 to 26 years HPV vaccine is also recommended for all females 19 to 26 years of age. (iv) Females aged 27 years and over Quadrivalent HPV vaccine is not registered for use in females over the age of 27 years as there are no safety or efficacy data to support its use in this age group. There is bridging immunogenicity data and safety data available for women up to the age of 55 for the bivalent vaccine. (v) Males Although quadrivalent HPV vaccine is licensed for use in males aged 9 to 15 years, vaccination of males is not recommended at this time due to the lack of clinical efficacy data. Although HPV vaccine produces high antibody titres in males, it is not known whether vaccination of males can either prevent transmission of HPV or provide protection against genital HPV infection, genital warts, anogenital dysplasia or anogenital cancers.	evidence are both either A or B. EFFICACY no data B A no data no data	
	Grade of recommendation	see above

Table 9: NHMRC - Assessing the body of evidence for HPV safety

Key question: Are VLP based HPV vaccines safe for use in humans? *(Circle appropriate grade for each component)*		Evidence table ref: Harro 2001 Evans 2001 Koutsky 2002 Ault 2004 Fife 2004 Harper 2004 Poland 2005 Villa 2005 Villa 2006 Harper 2006
1. Volume of evidence *(quantity, level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)*		
A: Several level II studies of high methodological quality and relevance to women aged 16–26 years (and some up to age 45, eg. Evans 2001, Harro 2001), with low risk of study bias. Although most (but not all) studies were sponsored by the vaccine developers, the quality and consistency of studies indicated a low risk of study bias. Only two Phase I studies (level II evidence but of limited sample size) (Harro 2001, Evans 2001) included males aged 18–45 years in whom the vaccine was well tolerated.	(A)	**Excellent** (several level I or II studies with low risk of bias)
	B	**Good** (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)
	C	**Satisfactory** (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)
	D	**Poor** (Level IV studies or Level I to III studies with high risk of bias)
2. Consistency *(the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group formed a judgement as to the overall direction of the evidence)*		
A: Several level II studies consistently demonstrated safety of human papillomavirus vaccines. There were no conflicting results regarding safety.	(A)	**Excellent** (all studies consistent)
	B	**Good** (most studies consistent and inconsistency can be explained)
	C	**Satisfactory** (some inconsistency, reflecting genuine uncertainty around question)

	D	**Poor** (evidence is inconsistent)
3. **Clinical impact** *(the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)*		
	A	**Excellent** (very large clinical impact)
B: HPV vaccines will have a substantial clinical impact in averting HPV related cervical dysplasia due to HPV16 and HPV18 and, in the case of the quadrivalent vaccine, genital warts. This benefit needs to be weighed against the occurrence of local injection site reactions, which will occur in most subjects but which will be of limited duration. There remains a risk of rare severe events such as anaphylaxis. Ongoing vaccine safety monitoring is required. There will be a continuing need for Pap screening programs due to the occurrence of disease due to HPV types not covered by the vaccines. The potential clinical impact will be largest in women who have not yet been exposed to/infected with HPV. This is women prior to first sexual activity and the most feasible proxy for this status is age. Thus the largest clinical impact will be in women aged 10–13 years, although the disease burden prevented through vaccination will not be achieved in this cohort until they become sexually active. Vaccination of women aged 14–18 and 19–26 years will prevent disease sooner, although the overall clinical impact in terms of disease reduction within those age cohorts will be lower than that achievable in the youngest cohort as some women will already be infected with HPV types covered by the vaccine. Duration of immunity is at least 5 years but requires ongoing monitoring in order to implement booster vaccination if needed. The potential clinical impact in males is not known due to an absence of efficacy data in males.	B	**Good** (substantial clinical impact)
	C	**Satisfactory** (moderate clinical impact)
	D	**Poor** (slight or restricted clinical impact)
4. **Generalisability** *(how reasonable is it to generalise from the results of the studies used as evidence to the target population for this guideline?)*		
	A	**Excellent** (directly generalisable to target population)
B: Populations studied are similar to the Australian target population. Australian subjects participated in one trial. However, exclusion criteria for trials included women with 4 or more sexual partners and a past history of Pap test abnormalities or genital warts. Median number of lifetime sexual partners in Australian women varies by age: 2.0 for women aged 16–19 and over 4 for women aged 20–49. Therefore, many Australian women have a higher probability of prior HPV infection with vaccine types than women in the trials, and therefore, vaccine effectiveness in the population can be expected to be lower than the efficacy achieved in the trials.	B	**Good** (directly generalisable to target population with some caveats)
	C	**Satisfactory** (not directly generalisable to the target population but could be sensibly applied)
	D	**Poor** (not directly generalisable to target population and hard to judge whether it is sensible to apply)

5. Applicability *(the extent to which the body of evidence is directly applicable to Australian healthcare context)*		
	A	**Excellent** (directly applicable to Australian healthcare context)
B: Highly applicable particularly given the high levels of participation in the National cervical screening program, although the program recommends less frequent screening than conducted in the trials. Vaccine safety monitoring in Australia is conducted through passive surveillance.	(B)	**Good** (applicable to Australian healthcare context with few caveats)
	C	**Satisfactory** (probably applicable to Australian healthcare context with some caveats)
	D	**Poor** (not applicable to Australian healthcare context)

6. Other factors	
Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation) Larger safety databases continuously updated with all trial participants' details are held by the vaccine manufacturers. Current data (as at the time of submission of the vaccines for review) was made available and also supported the safety of HPV vaccines in humans. Similar data for the quadrivalent vaccine is now published at the FDA website (U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee meeting May 18, 2006. Briefing information. 2006. http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm(accessed Jun 2006)), at the European Medicines Agency website (http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm (accessed Feb 2007)) and from Canadian NACI HPV Vaccine recommendations (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf (accessed March 2007)). No published studies of girls aged 10-15 years were identified in the body of this review but unpublished trial data, presented as commercial-in-confidence, and now publicly available (see Gardasil product information and references above), indicates equivalent tolerability to that observed in women aged 16-26 years. This data resulted in the upgrading of the safety recommendation in females 10 to 13 years. Unpublished trial data, presented as commercial in confidence, and now publicly available (see Gardasil product information and references above), indicates equivalent tolerability in males aged 9–15 years as that observed in women aged 16–26 years. This data resulted in the upgrading of the safety recommendation in males. In addition continued post-marketing surveillance (phase IV) studies will be ongoing and, specifically, linked registry studies are being conducted in some countries which will allow continuing assessments of safety and efficacy.	

EVIDENCE STATEMENT *Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.*			
The volume, consistency, clinical impact, generalisability and applicability of the body of evidence regarding the safety of human papillomavirus vaccines in humans are considered very good to excellent. All available data indicates that HPV vaccines are safe for use in humans. Strongest evidence for safety to date is in women aged 16–26 years who are the group for whom most published trial data is available. However some safety data (commercial-in-confidence at the time of assessment and now with some availability (see 'Other factors' above)) is available down to age 9 for the quadrivalent vaccine and age 10 for the bivalent vaccine and up to age 55 for the bivalent vaccine. There is some safety data available for males. There is data to indicate that vaccines are safe for use in those previously exposed to HPV. Studies to date have been powered to detect adverse events occurring with a frequency of 1 in several thousand. Thus, ongoing surveillance is essential to ensure that any rarer adverse reactions to vaccination are detected.	Component	Descriptor	Grade
	Volume of evidence	Excellent	A
	Consistency	Excellent	A
	Clinical impact	Good	B
	Generalisability	Good	B
	Applicability	Good	B
RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence?* (i) Females aged 10 to 13 years HPV vaccine is recommended for females 10 to 13 years of age. (ii) Females aged 14 to 18 years HPV vaccine is also recommended for females 14 to 18 years of age. (iii) Females aged 19 to 26 years HPV vaccine is also recommended for females 19 to 26 years of age. (iv) Females aged 27 years and over Quadrivalent HPV vaccine is not registered for use in females over the age of 27 years as there are no safety or efficacy data to support its use in this age group. Safety data for the bivalent vaccine Cervarix (not yet registered at time of writing) supports the safety of the bivalent vaccine up to age 55 in women.	The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B. SAFETY B A A bivalent vaccine – B quadrivalent vaccine – no data		

(v) Males Although quadrivalent HPV vaccine is licensed for use in males aged 9–15 years, vaccination of males is not recommended at this time due to the lack of clinical efficacy data. Available safety data suggests equivalent tolerability in males aged 9–15 years to that observed in females.	9-15 years – B other ages - no data	
	Grade of recommendation	see above