

# 2012 Antigen Review for the New Zealand National Immunisation Schedule: Human papillomavirus

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# Executive summary

This report summarises new research into human papillomavirus (HPV) vaccines and vaccination published during the past four years (2009-2013).

Most HPV infections are cleared within 18 months. However, clearing an infection does not necessarily lead to immunity and reinfection is possible. HPV types 6 and 11 account for around 90% of all genital warts cases and can also cause recurrent respiratory papillomatosis.

The casual link between human papillomaviruses and cervical cancer was made in the 1980s. Since then, it has been shown that virtually all cervical cancers could be attributed to the sexual transmission of around 12 oncogenic types, in particular HPV types 16 and 18. In countries without effective cervical screening programmes, cervical cancer is a leading cause of cancer death. It is now also recognised that these high risk HPV types are associated with anal cancer, vulvar cancer, vaginal cancer, penile cancer and HPV-positive oropharyngeal cancer.

In 2009, there were 107 cases of cervical cancer, accounting for 1.5% of female cancer registrations and 1.1% of female cancer deaths in New Zealand (NZ); it is the third most common cancer by incidence and fifth most common cancer mortality among NZ women. A further 185 cases of other cancers, including those affecting males, which were likely to be associated with the HPV-16 and -18 were also registered. Overall, an estimated 292 cases of cancer in 2009 were potentially preventable by vaccination against HPV-16 and -18.

The relatively low rate of cervical cancer registrations compared with other cancers is largely attributable to the cervical screening programme. Ethnic disparities in cancer registrations and mortality still existed in 2009; however, disparity in mortality had reduced.

Since 2007, two vaccines (HPV2 and HPV4) have been available to prevent infection by some HPV types. Both vaccines protect against HPV-16 and -18, and the quadrivalent vaccine (HPV4) also protects against HPV-6 and -11. Vaccination against human papillomavirus has the potential to reduce both the incidence of associated cancers and with respect to the HPV4 vaccine, HPV associated genital warts. Both vaccines are highly immunogenic in virtually all vaccinees and highly efficacious against persistent infection and cervical disease in recipients previously uninfected. However, the vaccines are not able to prevent disease caused by existing infection. For this reason, it is recommended that vaccination occurs prior to the onset of sexual activity.

New Zealand introduced an HPV immunisation programme in September 2008, providing a funded vaccine to girls and young women born in 1990 and 1991. The programme was extended in 2009 to girls and women born from 1992. The routine programme is offered primarily through a school-based programme to girls in year eight (aged 12 – 13 years). Decreases in new cases of genital warts in women under 20 years of age were already being observed by Auckland Sexual Health Service by 2010.

The impact of HPV4 vaccine on new cases of genital warts has been observed in many countries who have introduced the vaccine, including NZ. Generally, reductions are most profound in the population targeted by vaccination programmes, and to a significant but lesser extent, the population forming their sexual partners. Sexual health clinics in Melbourne, Australia have observed a near elimination of new cases of genital warts in their female population under 25 years of age and note that the reproduction number may have fallen below one. This means that genital warts could well be eradicated among this population. In contrast there have been no changes in the incidence of new cases of genital warts observed in older women or men who have sex with men – those populations not targeted for vaccination and their sexual partners. The reduction in prevalence in infections caused by the vaccine-types of HPV provides further support for the role of herd immunity provided by HPV vaccination.

The safety of HPV vaccines was evaluated in very large randomised placebo controlled trials, and reactogenicity and safety are well established. The past four years has focused on close monitoring of post licensure surveillance for events too rare to be detected in the pivotal studies. Extensive data, from very large populations that includes data for millions of vaccinees world wide, support the excellent safety profiles of these vaccines. Post marketing surveillance systems globally continue to monitor the safety of HPV vaccination programmes.

Both HPV vaccines are highly immunogenic. To date, anamnestic responses have been demonstrated in vaccine recipients out to 8.5 years. There is no evidence of waning immunity. HPV2 vaccine induces a more robust immune response than HPV4 against types 16 and 18. The clinical importance of this is not known; however, there appears to be superior cross-protection against non-vaccine oncogenic types offered by the bivalent vaccine. The value of this additional protection against cancer causing HPV types needs to be weighed against the impact on genital warts offered by HPV4.

Vaccination of women who have had procedures for pre-existing cervical diseases has been shown to be beneficial through a reduction in subsequent procedures. Very few women are co-infected with multiple vaccine types at any one time. As the only women who can derive no protection from vaccination are those already infected with all vaccine types, there are no benefits to screening prior to vaccination. Vaccination of older women is efficacious.

The vaccination of males, including those with HIV infection, has been demonstrated to be efficacious against HPV-associated cancers and genital warts. Currently, men who have sex with men are deriving no benefit from vaccination programmes that target only females.

Modelling the impact of HPV vaccination against cervical cancer supports vaccinating at an early age prior to sexual debut and vaccinating males, particularly if coverage of females is relatively low. Of particular relevance to NZ is the very early age of sexual debut reported. Data from the NZ Youth 2007 survey indicates over 20% of NZ adolescents have had sexual intercourse before the age of 13 years. This had increased to nearly 40% by the age of 15 years and over 50% by age 17 years. Rates are higher for Māori. Most HPV infections occur within the first two years of onset of sexual activity with more than 40% becoming infected during this period. As the first sexual relationship carries a substantial risk of exposure to HPV an important point to consider for the NZ schedule is timing, and consideration should be given to bringing the age for vaccination forward to include more girls prior to onset of first sexual activity.

There are no further vaccine options other than HPV2 and HPV4 available at this time. A nine-valent vaccine has completed phase III studies and results are anticipated.

The co-administration of HPV vaccine with other vaccines has been shown to be safe and immunogenic. The non-inferiority of a two-dose schedule in the younger age group noted to date is worthy of consideration and the flexibility of schedules may make programme delivery easier.

# **2012 Antigen Review for the New Zealand National Immunisation Schedule: Human papillomavirus**

Prepared as part of a Ministry of Health contract

by

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

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# Contents

<b>Executive summary .....</b>	<b>iii</b>
<b>1. Background – human papillomavirus and vaccination .....</b>	<b>1</b>
<b>2. Methodology for review.....</b>	<b>2</b>
2.1 Objectives .....	2
2.2 New Zealand epidemiology.....	2
2.3 Literature search strategy.....	2
2.3.1 Medline search terms and strategy .....	3
2.3.2 Cochrane Library search terms and strategy .....	3
2.3.3 Scopus search terms and strategy.....	3
2.3.4 Grey literature.....	3
2.3.5 Additional searches.....	3
2.3.6 Final library .....	3
2.4 Participants/populations .....	4
2.5 Interventions .....	4
2.5.1 Quadrivalent human papillomavirus vaccine.....	4
2.5.2 Bivalent human papillomavirus vaccine .....	4
2.6 Study designs.....	4
<b>3. Recent New Zealand epidemiology.....</b>	<b>5</b>
3.1 Human papillomavirus associated cancers .....	5
3.2 Genital warts .....	6
3.2.1 National trends .....	6
3.2.2 Gender, age and ethnic distribution.....	6
3.3 Summary of New Zealand epidemiology .....	9
<b>4. Safety.....</b>	<b>10</b>
4.1 Objective .....	10
4.2 Outcomes .....	10
4.3 Review .....	10
4.3.1 Safety of quadrivalent human papillomavirus vaccine.....	10
4.3.2 Safety of bivalent human papillomavirus vaccine.....	10
4.4 Summary vaccine safety .....	11
<b>5. Immunogenicity, efficacy, effectiveness and vaccine impact.....</b>	<b>12</b>
5.1 Objective.....	12
5.2 Outcomes .....	12
5.3 Review .....	12
5.3.1 Immunogenicity .....	12
5.3.2 Protection against disease outcomes.....	12
5.3.3 Herd immunity .....	16
5.3.4 Effect on prevalence of infection .....	16
5.3.5 Cross protection.....	16
5.3.6 Duration of protection .....	17

5.3.7 Vaccine performance in women aged 24 – 45 years .....	17
5.3.8 Vaccine performance in males .....	17
5.4 Summary of effectiveness .....	18
<b>6. Age-specific issues .....</b>	<b>19</b>
6.1 Objective .....	19
6.2 Review .....	19
6.2.1 Onset of sexual activity .....	19
6.2.2 Vaccine issues for different age groups .....	19
6.2.3 Optimal age for vaccination .....	19
6.3 Summary of age-specific issues .....	19
<b>7. Vaccine options .....</b>	<b>20</b>
7.1 Objective .....	20
7.2 Review .....	20
7.2.1 Second generation vaccines .....	20
7.3 Summary for vaccine options .....	20
<b>8. Options for scheduling .....</b>	<b>21</b>
8.1 Objective .....	21
8.2 Outcomes .....	21
8.3 Review .....	21
8.3.1 Number of doses .....	21
8.3.2 Alternative schedules .....	21
8.3.3 Use of human papillomavirus vaccine in males .....	22
8.4 Summary of schedule options .....	22
<b>9. Implementation issues .....</b>	<b>23</b>
9.1 Objective .....	23
9.2 Review .....	23
9.3 Summary for implementation issues .....	23
<b>10. International policy and practice .....</b>	<b>24</b>
10.1 Objective .....	24
10.2 Review .....	24
10.2.1 United States .....	24
10.2.2 European countries .....	24
10.2.3 Australia .....	24
10.3 Summary of international policy and practice .....	24
<b>11. References .....</b>	<b>25</b>

## Figures

Figure 1.	Flow of selection of articles for review .....	3
Figure 2.	Number of genital warts (first presentation) cases in sexual health clinics by age group for females .....	7
Figure 3.	Number of genital warts (first presentation) cases in sexual health clinics by age group for males .....	7
Figure 4.	Number of genital warts (first presentation) cases in family planning clinics by gender and age-group, 2006 – 2011 .....	8
Figure 5.	Number of genital warts (first presentation) cases reported from sexual health clinics by ethnicity, 2008 – 2011.....	8
Figure 6.	Number of genital warts (first presentation) cases reported from family planning clinics by ethnicity, 2008 – 2011.....	8
Figure 7.	Proportion of patients aged <21 years, diagnosed as having genital warts by risk group compared with men who have sex with men of all ages (42). .....	14
Figure 8.	Proportion of people presenting to sexual health services in Australia with genital warts, 2004 – 09 (6).....	15

## Tables

Table 1.	Numbers of registrations of and deaths from cervical cancer, by ethnicity, 1999 – 2009.....	5
Table 2.	Number of incident cancers in New Zealand in 2009 potentially preventable by vaccination.....	6
Table 3.	Trends in national totals of genital warts case counts.....	6
Table 4.	Number and percentage of first-visit clients diagnosed with genital warts by year and for first six months of 2010 [reprinted with permission (7)] .....	16
Table 5.	Efficacy against persistent infection with non-vaccine type human papillomaviruses (adapted from (45) .....	17
Table 6.	Efficacy against cervical intraepithelial neoplasia grade two or worse (CIN2+) with non-vaccine type human papillomaviruses (adapted from (45) .....	17



## Abbreviations

ACIP	Advisory Committee on Immunization Practices (US)
AEFI	Adverse event following immunisation
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
CI	Confidence interval
CIN1	Cervical intraepithelial neoplasia grade 1
CIN2+	Cervical intraepithelial neoplasia grade 2 or worse
CIN3+	Cervical intraepithelial neoplasia grade 3 or worse
ELISA unit	Enzyme-linked immunosorbent assay unit, a unit of measure for antigen content
ESR	The Institute of Environmental Science and Research
FDA	U.S. Food and Drug Administration
FPC	Family planning clinic
FUTURE I	Females United to Unilaterally Reduce Endo/Ectocervical Disease I study
FUTURE II	Females United to Unilaterally Reduce Endo/Ectocervical Disease II study
GMT	Geometric mean titre
GP	General Practitioner
HGAIN	High grade anal intraepithelial neoplasia
HPV	Human papillomavirus
HPV2	Bivalent HPV vaccine, Cervarix® (types 16 and 18)
HPV4	Quadrivalent HPV vaccine, Gardasil® (types 6, 11, 16 and 18)
MSM	Men who have sex with men
n	Number of study participants
NZ	New Zealand
PATRICIA	Papilloma Trial against Cancer In young Adults
QALYs	Quality-adjusted life years
SAE	Serious adverse event
STI	Sexually transmitted infection
SHC	Sexual health clinic
SYHC	Student and youth health clinic
US	United States
VLP	Virus-like particle
WHO	World Health Organization

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# 1. Background – human papillomavirus and vaccination

Genital human papillomavirus (HPV) infections are transmitted primarily, although not exclusively, by sexual contact. Human papillomaviruses are highly transmissible. Most sexually active women and men will acquire infection with at least one type at some point, usually soon after sexual debut. Most infections are benign and transient; however, development of a persistent infection with certain high risk types can lead to a range of anogenital pre-cancers and cancers. Annually, there are around half a million new cases of cervical cancer and quarter of a million related deaths worldwide. Countries that have effective programmes in place to detect and treat precancerous abnormalities can prevent the development of most cancers.

The casual link between human papillomaviruses and cervical cancer was made in the 1980s when Harald zur Hausen identified the presence of HPV DNA in the majority of cervical cancers (1). Later studies showed that virtually all cervical cancers could be attributed to the sexual transmission of around 12 oncogenic types, in particular, HPV-16 and -18. In the absence of effective cervical screening programmes, cervical cancer is a leading cause of cancer death worldwide. It is now known that these high risk HPV types are also associated with anal cancer, vulvar cancer, vaginal cancer, penile cancer and HPV-positive oropharyngeal cancer.

HPV-6 and -11 account for around 90% of all genital warts cases and can also cause recurrent respiratory papillomatosis.

Most HPV infections are cleared within 18 months. Clearing an infection does not necessarily lead to immunity and reinfection is possible.

Since 2007, there have been two vaccines available to prevent infection by some HPV types. Both vaccines protect against HPV-16 and -18; a four valent vaccine (HPV4) also protects against HPV-6 and -11. While both vaccines are highly immunogenic in virtually all vaccinees, and highly efficacious in recipients previously uninfected, they are not able to prevent disease caused by existing infection. For this reason, it is recommended that vaccination occurs prior to the onset of sexual activity. In 2009, the World Health Organization (WHO) recommended that routine HPV vaccination should be included in national immunisation programmes for girls from age nine to 13 years where possible, sustainable and practical.

Vaccination against HPV has the potential to reduce both the incidence of associated cancers and with respect to the HPV4 vaccine, HPV-associated genital warts.

New Zealand (NZ) introduced an HPV immunisation programme in September 2008 which provided funded vaccine to girls and young women born in 1990 and 1991. The programme was extended in 2009 to girls and women born from 1992. The routine programme is offered primarily through a school-based programme in year eight (aged 12 - 13 years). Decreases in new cases of genital warts in women under 20 years of age were already being observed by Auckland Sexual Health Service in 2010.

This report summarises new research into HPV vaccines and vaccination published during 2009 to 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

# 2. Methodology for review

## 2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for human papillomavirus vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around human papillomavirus vaccines for New Zealand.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options
- Specific service specifications for human papillomavirus vaccines
  - Evidence for including boys on the schedule, including genital wart data and considerations.
  - Emerging HPV vaccines and different vaccine options, including new multivalent HPV vaccines.
  - Evidence regarding duration of protection.
  - International evidence for the best cut-off age for offering the vaccine.
  - Duration of protection provided by vaccines.

## 2.2 New Zealand epidemiology

The most recent data, as of 2009, for the number of cases and rates of HPV-related cancers was sourced from the New Zealand Cancer Registry and published by the Ministry of Health in 2012 (2).

The data for trends in genital warts has been sourced from the Sexually Transmitted Infections in New Zealand: Annual Surveillance Report 2011 prepared by The Institute of Environmental Science and Research Ltd (ESR) (3). At the time of this report the 2012 data was not available.

It is important to note that the sexual health report summarises the epidemiology of sexually transmitted infections (STI), using data from sexual health clinics (SHC), family planning clinics (FPC), student and youth health clinics (SYHC) and diagnostic laboratories in NZ. The figures presented may underestimate true infection rates, because not all clinics and laboratories report to ESR and STIs are also diagnosed by a range of other healthcare providers, such as general practitioners who do not report to ESR. It is also important to note the denominator used in calculating disease rates: rates based on clinic data use the total number of clinic visits as the denominator, whether for STIs or other conditions; rates based on laboratory data use the total 'usually resident' population, in the District Health Boards covered by laboratory surveillance from the 2006 New Zealand Census.

## 2.3 Literature search strategy

The points below have formed the focus of the literature search:

- Safety
- Effectiveness in disease control
  - Effect on
    - Indirect effects/herd immunity
    - Duration of protection
  - Immunogenicity
- Implementation issues (practicality of and possible impact on uptake)

- Differences that need to be considered for each age group, and groups with particular needs
  - Age
  - High-risk groups – definition of which groups most likely to benefit and which vaccine/s
- Different options for placement on the schedule, based on international findings and best practice
- Different vaccine options and comparison between the options
- Current international research and evidence around use of vaccines

#### Other areas of special interest

- Evidence for including boys on the schedule
- Review of genital wart data
- Emerging HPV vaccines and different vaccine options, including new multivalent HPV vaccines
- Optimal age for vaccination and cut-off age for offering the vaccine
- Duration of protection provided by vaccines

### 2.3.1 Medline search terms and strategy

#### MeSH term: Papillomavirus vaccines

3384

Limit to Humans, English, 2009 – current

1793

NOT Costs and Cost analysis

1514

NOT qualitative, interview, parent, physician, survey, attitudes

1084

#### MeSH term: AND Adverse Effects OR safety

135

71 (keep and view)

#### MeSH term: AND Effectiveness OR efficacy

177

71 (keep and view)

### 2.3.2 Cochrane Library search terms and strategy

Search term Human papillomavirus Vaccin\*

Limit to Cochrane Reviews, Other Reviews, and Trials 2009 – present

5 results (keep and view)

### 2.3.3 Scopus search terms and strategy

Human papillomavirus Vaccin\* Published 2011 – present

1830

Limit to: Medicine, humans, vaccination, human papillomavirus vaccine, journals

Exclude Letter, Short survey, editorial and erratum

682

16 (keep and view)

Reject social science articles. Delete duplicates

#### Final EndNote library after literature search and revisions 219

### 2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012. No abstracts or posters were accessed. Four reports and two data sheets were accessed.

### 2.3.5 Additional searches

Where questions arose, additional searches were undertaken to ensure there was no further available data. Missing articles were accessed and added to the library. A further nine articles were accessed.

### 2.3.6 Final library

The final library includes 234 references. Where systematic reviews and/or meta-analysis were available, the preceding literature has been excluded from the review.

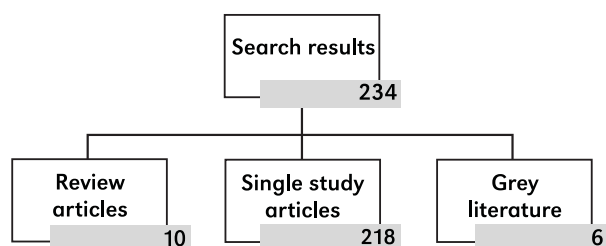


Figure 1. Flow of selection of articles for review

## 2.4 Participants/populations

The population for a potential universal programme are school-aged children in year seven.

## 2.5 Interventions

The interventions included are:

- Quadrivalent human papillomavirus vaccine (HPV4)
- Bivalent human papillomavirus vaccine (HPV2)

### 2.5.1 Quadrivalent human papillomavirus vaccine

The licensed HPV4 vaccine, Gardasil® (Merck and Co Inc.), is a recombinant vaccine. The genes for the major capsid protein (L1) of HPV-6, -11, -16 and -18 have been expressed in *Saccharomyces cerevisiae* (yeast). The proteins self-assemble into conformationally intact, non-infectious virus-like particles (VLPs) and are then adsorbed on to aluminium adjuvant. Each 0.5mL dose contains HPV-6 (20µg), -11 (40µg), -16 (40µg) and -18 (20µg) L1 proteins and amorphous aluminium hydroxyphosphate sulphate (225µg). The formulation also includes sodium chloride, L-histadine, polysorbate 80, sodium borate and water for injection. Residual yeast protein may be present from the manufacturing process (4).

### 2.5.2 Bivalent human papillomavirus vaccine

The licensed HPV2 vaccine, Cervarix® (GlaxoSmithKline), is a recombinant vaccine. The genes for the major capsid protein (L1) of HPV-16 and -18 have been produced using the recombinant Baculovirus expression vector system and expressed in *Trichoplusia ni* insect cells. The proteins self-assemble into conformationally intact, non-infectious VLPs and are then adsorbed on to the AS04 adjuvant system, which is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on to aluminium as hydroxide salt. Each 0.5mL dose contains HPV-16 (20µg) and -18 (20µg) L1 proteins, MPL (50µg), aluminium hydroxide (0.5mg), sodium chloride (4.4mg) and sodium dihydrogen phosphate dehydrate (0.624mg). The vaccine may contain residual amounts of insect cell and viral protein (<40ng) and bacterial cell protein (<150ng) from the manufacturing process (5).

## 2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials and observational studies using database matching. Conference abstracts have also been added.

# 3. Recent New Zealand epidemiology

## 3.1 Human papillomavirus associated cancers

The New Zealand Cancer Registry receives and collates data on cases of primary malignant tumours diagnosed in NZ. The major sources are laboratory reports, post discharge reports from public hospitals, discharge reports from private hospitals, death certificates and autopsy reports. The most recent data from 2009 was published in 2012 (2).

In 2009, cervical cancer accounted for 141 cancer registrations equating to 1.5% of all female cancer registrations. There were 44 cervical cancer related deaths accounting for around 1.1% of all cancer deaths in women. There is considerable disparity in registrations between ethnic groups, with Māori more than double that of non-Māori. Mortality from cervical cancer among Māori women is nearly three times that of non-Māori (caution as these are small numbers). There has been a downward trend in cervical cancer registrations in the ten years between 1999 and 2009 and the death rates has more than halved. The ethnic disparities in registrations are unchanged but disparities in mortality have narrowed.

The numbers and registrations and deaths for cervical cancer are listed in Table 1.

**Table 1. Numbers of registrations of and deaths from cervical cancer, by ethnicity, 1999 – 2009**

	Registrations			Deaths		
	Total	Māori	Non-Māori	Total	Māori	Non-Māori
1999	220	43	177	71	20	51
2000	204	43	161	66	17	49
2001	189	33	156	63	13	50
2002	181	33	148	65	12	53
2003	178	33	145	58	8	50
2004	157	33	124	71	15	56
2005	154	25	129	54	13	41
2006	160	29	131	52	10	42
2007	159	33	126	65	11	54
2008	175	37	138	59	12	47
2009	141	29	112	44	9	35

Source: New Zealand Cancer Registry and New Zealand Mortality Collection

Data on the number of cervical cancers potentially preventable by HPV vaccination in 2009 has been estimated by scientists at CSL Limited based on the proportion of genital, anal and oropharyngeal cancers that are associated with HPV vaccine types internationally and the number of cases in NZ during that year. These data are presented in Table 2.

**Table 2. Number of incident cancers in New Zealand in 2009 potentially preventable by vaccination**

	Women (n)	Men (n)	% of cases associated with HPV	% of HPV associated cases due to HPV-16 and -18	Cases potentially preventable by HPV 16/18 vaccine	
					Women (n)	Men (n)
Cervical cancer	141	-	100%	76%	107	-
Vulval cancer	51	-	40%	86%	18	-
Vaginal cancer	21	-	70%	88%	13	-
Penile cancer	-	7	50%	87%	-	3
Anal cancer	29	21	85%	93%	23	17
Cancer of the base of tongue and oropharynx	47	132	66%	94%	29	82
<b>Total</b>	<b>289</b>	<b>160</b>			<b>190</b>	<b>102</b>

## 3.2 Genital warts

### 3.2.1 National trends

There were a total of 2,905 cases of first presentation of genital warts reported in 2011. This is based on the total cases reported from SHC, FPC and SYHC. Clearly, this is a significant underestimation as it does not include all other avenues for presentation, particularly at general practice. The total number of clinic visits for each type of centre has remained relatively stable over the past 11 years, with the exception of student and youth health clinics, where usage has been increasing since 2005. This is attributed to the addition of clinics in Victoria and Otago Universities.

There was a decreasing trend in the number of cases of genital warts presenting to all clinics reporting between 2008 and 2011 (Table 3). This decrease was most notable in females aged 15 – 19 years of age, corresponding to the HPV immunisation programme introduced in 2008 targeting that population. This supports the findings of ecological studies in Auckland and Australia, which observed a decline in the proportion of new clinic patients diagnosed with genital warts in populations targeted by immunisation programmes (6, 7). Investigation to quantify the effectiveness of the vaccination programme in NZ, comparing genital warts rates in vaccinated and unvaccinated populations, would provide additional evidence to support the observed trend.

**Table 3. Trends in national totals of genital warts case counts**

	2006	2007	2008	2009	2010	2011
Sexual health clinics	3201	3797	3726	3290	2772	2469
Family planning clinics	611	621	573	546	302	276
Student and youth health clinics	206	201	243	245	182	160
<b>TOTAL</b>	<b>4018</b>	<b>4619</b>	<b>4542</b>	<b>4081</b>	<b>3256</b>	<b>2905</b>

### 3.2.2 Gender, age and ethnic distribution

#### 3.2.2.1 Gender

More cases of genital warts were seen in males than females at SHC (54.3%, 1340/2469). In contrast, more cases of genital warts were seen in females than males at FPC (67.4%, 186/276) and SYHC (61.9%, 99/160). This data very likely reflects usage patterns of services rather than actual sexual differences in genital wart distribution.

### 3.2.2.2 Age

In SHC, 50.7% (1252/2469) of the reported cases of genital warts were in persons aged less than 25 years. The proportion of cases aged under 25 years was larger in FPC (75.7%, 209/276) and SYHC (91.9%, 137/149) than in SHC. The mean age of cases of genital warts was 27.1 years in SHC, 22.4 years in FPC and 21.1 years in SYHC.

The number of males with genital warts was highest in the 20 – 24 years age group across all clinic types (445 cases in SHCs, 41 cases in FPC and 38 cases in SYHC). For females, case numbers were highest in the 15 – 19 years age group in FPC (75 cases), and in the 20 to 24 years age group in SHC (403 cases) and SYHC (58 cases). Figure 2, Figure 3 and Figure 4 present the number of genital warts cases reported by age group and sex for SHC and FPC from 2006 – 2011.

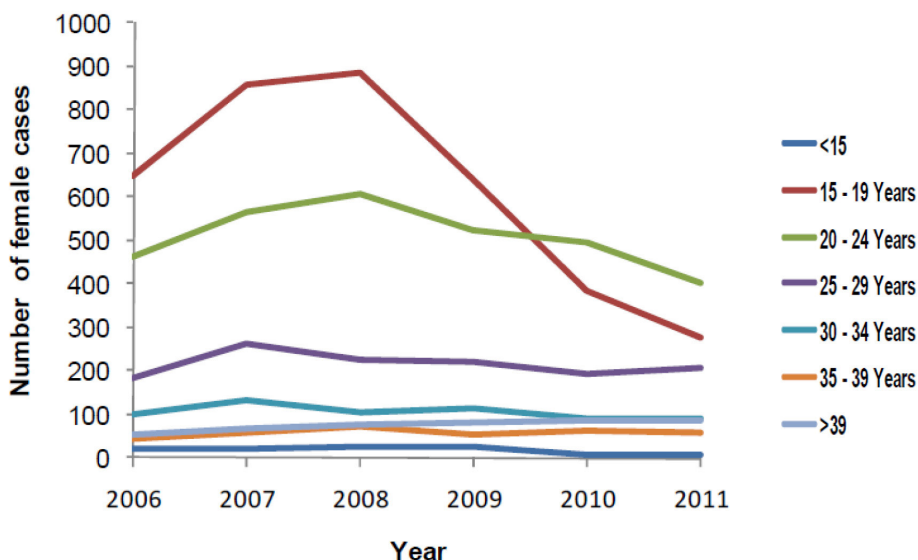


Figure 2. Number of genital warts (first presentation) cases in sexual health clinics by age group for females

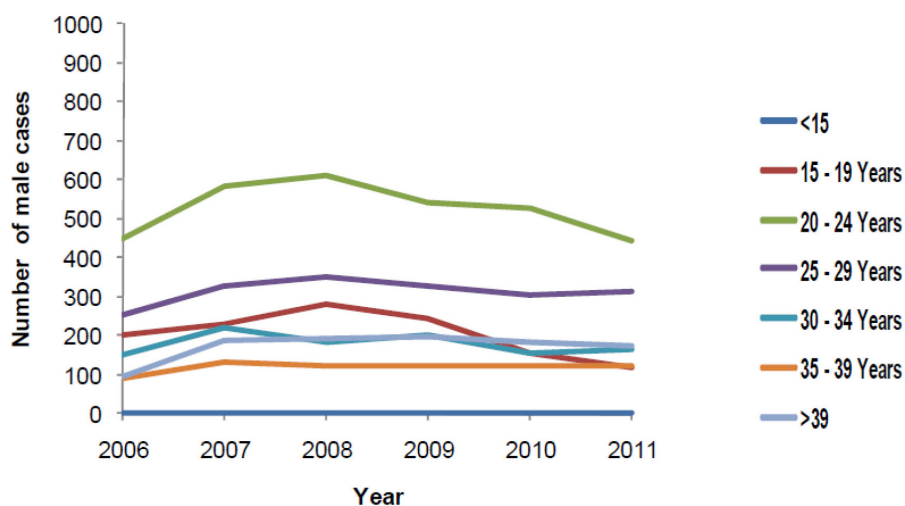


Figure 3. Number of genital warts (first presentation) cases in sexual health clinics by age group for males



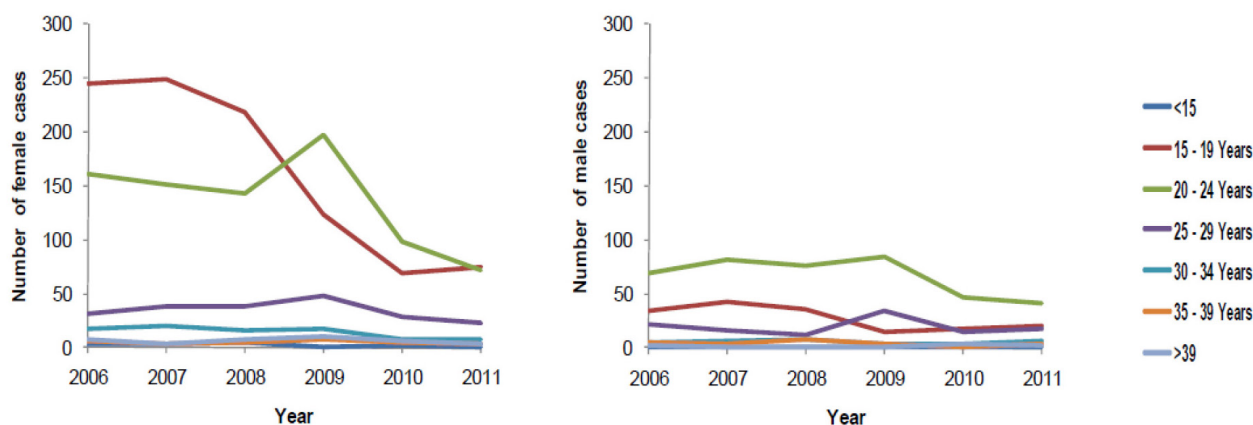


Figure 4. Number of genital warts (first presentation) cases in family planning clinics by gender and age-group, 2006–2011

### 3.2.2.3 Ethnicity

Ethnicity was recorded by SHC for 97.3% (2,402/2,469) of the reported cases. The highest percentage of cases reported by SHC were of European ethnicity (71.4%, 1,715 cases), followed by Māori (16.2%, 388 cases), Other (7.6%, 183 cases) and Pacific Peoples (4.8%, 116 cases) ethnicity. Ethnicity was recorded by FPC for 93.8% (259/276) of the reported cases. The highest percentage of cases reported by FPC were of European ethnicity (80.3%, 208 cases), followed by Māori (15.1%, 39 cases), and Pacific Peoples and Other (2.3%, 6 cases each) ethnicity. Ethnicity was recorded by SYHC for 96.9% (155/160) of the reported cases. The highest percentage of cases reported by SYHC were of European ethnicity (71.0%, 110 cases), followed by Māori (18.7%, 29 cases), Other (9.0%, 14 cases) and Pacific Peoples (1.3%, 2 cases) ethnicity. The trends for SHC and FPC from 2008 – 2011 are presented in Figure 5 and Figure 6.

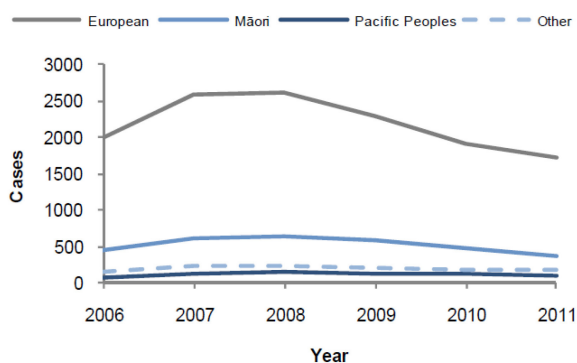


Figure 5. Number of genital warts (first presentation) cases reported from sexual health clinics by ethnicity, 2008–2011

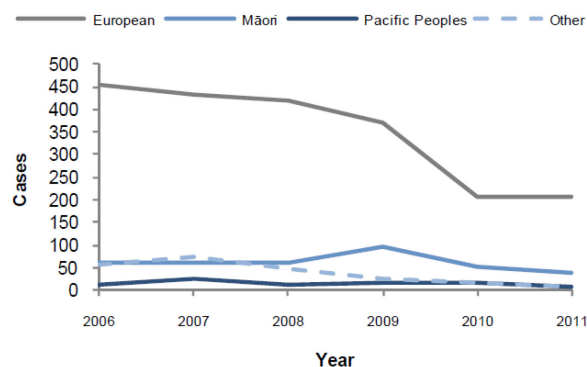


Figure 6. Number of genital warts (first presentation) cases reported from family planning clinics by ethnicity, 2008–2011

### 3.3 Summary of New Zealand epidemiology

The most recent data available for NZ cancer registrations is for 2009. There were 107 cases of cervical cancer, accounting for 1.5% of female cancer registrations and 1.1% of female cancer deaths. Ethnic disparities in registrations and mortality remained present from 1999 through to 2009. Although disparity in mortality reduced, mortality remained significantly higher in Māori women.

Several other cancers are associated with HPV-16 and -18, including vulval, vaginal, penile, anal and oropharyngeal cancers. In 2009, there were 185 cases of other cancers, including those affecting males, which were likely to be associated with the HPV-16 and -18. Overall, an estimated 292 cases of cancer were potentially partially or fully preventable by vaccination against HPV-16 and -18, as shown in Table 2.

Between 2006 and 2011, there was a notable decrease in the genital warts case numbers among females in SHC in the 15 – 19 years age group. Case numbers among males and females in the 20 – 24 years age group increased slightly in 2008, followed by decreases between 2009 and 2011. In FPC, notable decreases were observed among females in the 15 – 19 years age group, as well as in the 20 – 24 years age group. In SHC, there was peak in diagnoses in those of European, Māori and Pacific ethnicity in 2008. Since 2008, case numbers seen in each ethnic group have decreased annually. In FPC, the numbers diagnosed in every ethnic group have decreased since 2006.

There is clear evidence in data from 2010 and 2011 of an impact from the HPV vaccination programme, which commenced in 2008, on new cases of genital warts in females among the age group targeted for vaccination. There is also evidence of a reduction of genital warts among males in the 15 – 24 year age group.

# 4. Safety

## 4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed HPV vaccines. Only adverse events following immunisation that have been considered subsequent to the pivotal clinical efficacy trials will be reviewed here and any major clinical differences between vaccine types.

## 4.2 Outcomes

Outcomes are vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE). Excluded is reactogenicity (injection site reactions and minor systemic reactions) as these have been thoroughly considered in the pivotal licensure studies.

## 4.3 Review

### 4.3.1 Safety of quadrivalent human papillomavirus vaccine

Autoimmunity is a theoretical safety issue for any vaccine. As such conditions are relatively rare, risks need to be assessed during post-marketing surveillance studies. There are now several such studies published. By mid-2011, around 35 million doses of HPV4 vaccine had been distributed in the US alone. An observational study, undertaken in two managed care organisations in California, included 189,629 women who had received at least one dose of HPV4 vaccine between August 2006 and March 2008. Onset of potentially new conditions was sought and a background incidence estimated using data from unvaccinated women. No autoimmune signal was detected in this study (8).

No new safety concerns have been raised with regard to HPV4 since the pivotal clinical trials. Vaccination has been associated with same-day syncope and skin infections within two weeks of vaccination. However, reported skin-associated events are likely to have been injection site reactions rather than infections (9). Safety monitoring systems are in place globally and continue to monitor the vaccine (10-12).

#### 4.3.1.1 Safety in pregnancy

Although HPV vaccine is not recommended for use during pregnancy, there are many women who have been exposed while pregnant, both during the pivotal trials and subsequently since licensure. As both HPV vaccines are non-live vaccines, there is no theoretical risk to a pregnant woman or her infant. During the clinical trials, there were no differences in pregnancy or birth outcomes between women exposed to the vaccines and women who were given the placebos. Since licensure, a company run global pregnancy register has collected information about pregnant women exposed to the vaccines. Reports show that the rates of spontaneous abortions, birth defects and other outcomes are comparable to those in the general population. Data from the US, France and Canada show that for 517 prospective reports with known outcomes, 451 (87.2%) were live births, including three sets of twins. Of 454 neonates, 439 (96.7%) were normal. The overall rate of spontaneous abortion was 6.9 per 100 outcomes (95% CI 4.8 – 9.6). The prevalence of major birth defects was 2.2 per 100 live born neonates (95% CI 1.05 – 4.05). There were seven fetal deaths (1.5 per 100 outcomes, 95% CI 0.60 – 3.09) (13, 14).

Women exposed to HPV4 vaccine while pregnant passed vaccine-type antibodies to their infants (15).

#### 4.3.1.2 Concomitant use

Gardasil® administered concomitantly with conjugate meningococcal A,C,Y,W-135 (Menactra®) and Tdap (Adacel®) vaccines, Tdap-IPV (Repevax®) vaccine and Tdap (Boostrix®) and conjugate meningococcal A,C,Y,W-135 (Menveo®) vaccines is well tolerated and immunogenic (16-18).

### 4.3.2 Safety of bivalent human papillomavirus vaccine

#### 4.3.2.1 Concomitant use

HPV2 vaccine has been demonstrated safe (and immunogenic) when administered concomitantly with inactivated hepatitis A and B (Twinrix®) vaccine, Tdap-IPV (Boostrix®-IPV) vaccine, hepatitis B (Engerix®-B) vaccine and Tdap (Boostrix®) and conjugate meningococcal A,C,Y,W-135 (Menactra®) vaccines (19-22).

## 4.4 Summary vaccine safety

Both HPV vaccines have excellent safety profiles. There have been no safety signals raised since the vaccines were licensed and a number of large investigations have been carried out to assess specific outcomes, particularly autoimmune conditions. Post marketing surveillance systems globally continue to monitor the safety of HPV vaccination programmes.

# 5. Immunogenicity, efficacy, effectiveness and vaccine impact

## 5.1 Objective

The objective of this section is to review the most recent performance data for currently licensed HPV vaccines. Consideration will be given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of HPV vaccines and evidence of their impact in populations.

## 5.2 Outcomes

The outcomes considered for this review are:

Genital warts

Cervical cancer

Vulval, vaginal, penile, anal and oropharyngeal cancers

## 5.3 Review

### 5.3.1 Immunogenicity

There are a range of immune strategies employed by the host to resist, control and resolve infection with HPV. Each stage may require a different response. It is thought that innate immunity may be better at controlling infection after viral entry into epithelial cells and prevention of initial infection may depend on CD4+ T-cell immunity and high levels of neutralising antibodies. The relevant contributions of these immune components are still not well understood (23).

Both vaccines, HPV4 (Gardasil®) and HPV2 (Cervarix®), induce robust immune responses. Serum antibody responses have generally been the focus of immunological assessments. Antibody responses are induced in virtually all vaccine recipients. Levels increase after each dose and peak one month after the third dose. There is a rapid waning of titres over the next two years, and then stabilisation at a plateau, which is higher than that induced by natural infection. There is currently no correlate of protection for HPV. There is no evidence that, following vaccination with Gardasil®, protection wanes as a result of reduced antibody titres (24). Cervarix® induces significantly higher antibody titres than Gardasil®, however, there is no evidence that this translates to superior

protection and it remains to be seen if duration of protection is influenced (25).

Immunogenicity appears to be influenced by age, with younger girls (9 – 13 years) exhibiting as high an antibody response after two doses as young women (16 – 25 years) do after three doses (26-30). The duration of this immunity is not yet known.

The effect of age and number of doses on the immunogenicity of HPV4 has been assessed and younger age (9 – 13 years) was associated with superior B-memory cell responses and optimal memory cell induction was achieved after two doses administered at zero and six months (31).

Memory immune responses in women who received three doses of a monovalent HPV-16 vaccine in a phase II trial have been demonstrated out to 8.5 years following administration of the HPV4 vaccine as an antigen challenge (32).

Immunogenicity to four years has been demonstrated in adolescent girls (10 – 14 years) who received three doses of the HPV2 vaccine. Antibody titres were maintained at higher levels than those in young women in whom vaccine efficacy had been previously demonstrated (33).

Immunogenicity of HPV4 in males has been demonstrated to be comparable to women and seroconversion occurs in almost all subjects. In the US, black men had significantly higher antibody titres at month seven than either Caucasian or Asian men (34).

The HPV4 vaccine has been demonstrated to be safe and immunogenic in HIV-infected men (35).

### 5.3.2 Protection against disease outcomes

#### 5.3.2.1 Cervical disease

Modelling of the impact of HPV vaccination programs on the incidence of cervical cancer in France suggested a 32% reduction after 20 years and an 83% reduction after 50 years in the incidence of cervical cancers due to types 16 and 18. Attaining higher coverage and vaccinating girls before the age of 14 years indicated a better impact on cervical cancer incidence with a modest extra impact if men were vaccinated (36).

Prophylactic efficacy of HPV4 was evaluated in the pivotal Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II studies over 42 months. Efficacy was 95.9% (95% CI 91.3 – 98.4) against cervical intraepithelial neoplasia grade 1 (CIN1), associated with HPV-6, -11, -16 or -18 in the per-protocol HPV-naïve population (day one to month seven), and 100% for both vulvar and vaginal intraepithelial neoplasia grade 1 associated with HPV-6, -11, -16 or -18 (95% CI 74.1 – 100; 64.0 – 100, respectively). In the intention-to-treat population, vaccine efficacy against CIN1 associated with HPV-6, -11, -16 or -18 was 69% (95% CI 61.6 – 75.1), and 69.1% and 83.3%, respectively, against vulvar and vaginal intraepithelial neoplasia grade 1 associated with HPV-6, -11, -16 or -18 (95% CI 29.8 – 87.9; 51.3 – 95.8, respectively) (37).

The end of study results for Papilloma Trial against Cancer in young Adults (PATRICIA) show that HPV2 has very high efficacy against cervical intraepithelial neoplasia grade 3 or worse (CIN3+) and adenocarcinoma *in situ* (AIS). Efficacy against CIN3+ associated with HPV-16 and -18 was 100% (95% CI 85.5 – 100) in the HPV-naïve at baseline group and 45.7% (95% CI 22.9 – 62.2) in the total vaccinated cohort. Vaccine efficacy against all AIS was 100% (95% CI 31.0 – 100) and 76.9% (95% CI 16.0 – 95.8) in the HPV-naïve at baseline group and total vaccinated cohort, respectively (38).

#### 5.3.2.1.1 Subsequent disease after excisional procedure

Among 17,622 participants in the FUTURE I and II studies were 2,054 that had previously received cervical surgery, or were diagnosed with genital warts, vulvar intraepithelial neoplasia or vaginal intraepithelial neoplasia. Of these, 587 vaccine and 763 placebo recipients had undergone cervical surgery. In the vaccine group, the incidence of subsequent HPV-related disease was 6.6% and in the placebo group it was 12.2%. This was a reduction of 46.2% (95% CI 22.5 – 63.2) in the vaccine group. In addition, there were 229 vaccine recipients and 475 placebo recipients that were diagnosed with the other conditions previously. Among these groups, the incidence of subsequent disease was 20.1% in the vaccine group and 31% in the placebo group, a reduction of 35.2% (95% CI 13.8 – 51.8) in the vaccine group (39).

#### 5.3.2.1.2 Efficacy in women previously exposed to HPV

Evidence from the PATRICIA study for women with current or previous HPV infection showed that less than 1% of women were DNA positive for both HPV-16 and -18 and around 18 – 19% are positive for one or the other at the time of screening. As the only women who can derive no protection from vaccination are those who are currently infected with both HPV-16 and -18, there is no value in screening before vaccinating as these women are a very small proportion of the population.

#### 5.3.2.2 Genital warts

Prophylactic efficacy of HPV4 against genital warts was evaluated in the FUTURE I and II studies over 42 months. Efficacy against genital warts associated with HPV-6, -11, -16 or -18 in the per-protocol, HPV-naïve population (day one to month seven), was 99% (95% CI 96.2 – 99.9). In the intention-to-treat population, vaccine efficacy against genital warts associated with HPV-6, -11, -16 or -18 was 79.5% (95% CI 73.0 – 84.6) (37).

The relatively rapid development of genital warts following infection offers the ability to assess the early impact of HPV vaccination programmes. Reductions in new cases of genital warts have been reported from a number of countries, including NZ. These reductions reflect the cohort vaccinated and, to a lesser extent, their sexual contacts.

In Sweden, the HPV4 vaccine was made available in 2006 and subsidised in 2007 for girls aged 13 – 17, incurring some out-of-pocket costs. Coverage is estimated at around 25% of girls aged 13 – 20 for at least one dose and over 30% among girls aged 15 – 18 years. The incidence proportion for genital warts in Sweden was calculated using the entire population aged 10 – 44 years living in Sweden between 2006 and 2010. Genital wart episodes are reported to a national register. Between 2008 and 2010, the rates between males and females, which had previously been similar, diverged with the overall incidence in males increasing and the incidence among females decreasing, particularly among females less than 25 years of age. The crude incidence in males remained close to the reference of 1.00 ( $p=0.39$ ) while in females reduced to 0.83 ( $p<0.0001$ ) (40).

Trends in genital warts were assessed in California using clinical encounter claims data from the California Family Planning Access Care and Treatment programme. Around 1,754,000 female and 258,000 male clients are seen annually. Between 2007 and

2010, genital warts diagnosis decreased by 34.8% (95% CI 38.2 – 31.5) among female clients younger than 21 years of age. Decreases were also observed among males younger than 21 years (19%), and females and males aged 21 – 25 years (10% and 11%, respectively). Among older age groups diagnosis was either stable or increased (41).

Australia was the first country to introduce a fully funded HPV programme and offered the vaccine for girls aged 12 – 17 from April 2007 and up to 26 years of age from July 2007. Since this time there has been a near disappearance of new cases of genital warts among women and men less than 21 years of age presenting to the Melbourne Sexual Health Centre. In women aged less than 21 years, annual cases have dropped from a mean of 56 per annum to just four for the 2010/2011 period. A similar reduction has been observed for men who have sex with women in this age group (Figure 7). In addition, the data indicate that the basic reproductive rate has now fallen below one. The heterosexual transmission of HPV- 6 and -11 causing genital warts in Australia is expected to become rare as a result of the HPV vaccination programme (42).

In addition to local studies, such as at the Melbourne Sexual Health Centre, Australia established a national surveillance network to identify trends in diagnoses of genital warts from 2004 – 2009. Among 112,083 new patients attending sexual health services, 9,867 (9%) cases of genital warts were identified. Before the vaccine programme started, there was no change in proportion of women or heterosexual men diagnosed with genital warts. After vaccination began, a decline in number of diagnoses of genital warts was noted for young female residents (59%,  $p_{\text{trend}} < 0.0001$ ). No significant decline was noted in female non-residents, women older than 26 years in July, 2007, or in men who have sex with men (MSM). However, proportionally fewer heterosexual men were diagnosed with genital warts during the vaccine period (28%,  $p_{\text{trend}} < 0.0001$ ), and this effect was more pronounced in young men. By 2009, 65.1% of female Australian residents who were eligible for free vaccine reported receipt of a quadrivalent or unknown HPV vaccine (6). The proportion of people presenting to the Australian Sexual Health Centres with genital warts are presented by age and risk group in Figure 8.

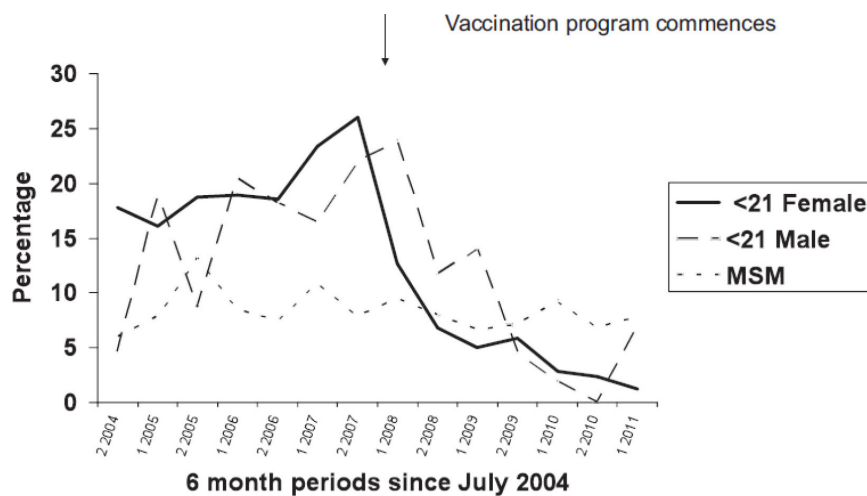


Figure 7. Proportion of patients aged <21 years, diagnosed as having genital warts by risk group compared with men who have sex with men of all ages (42).



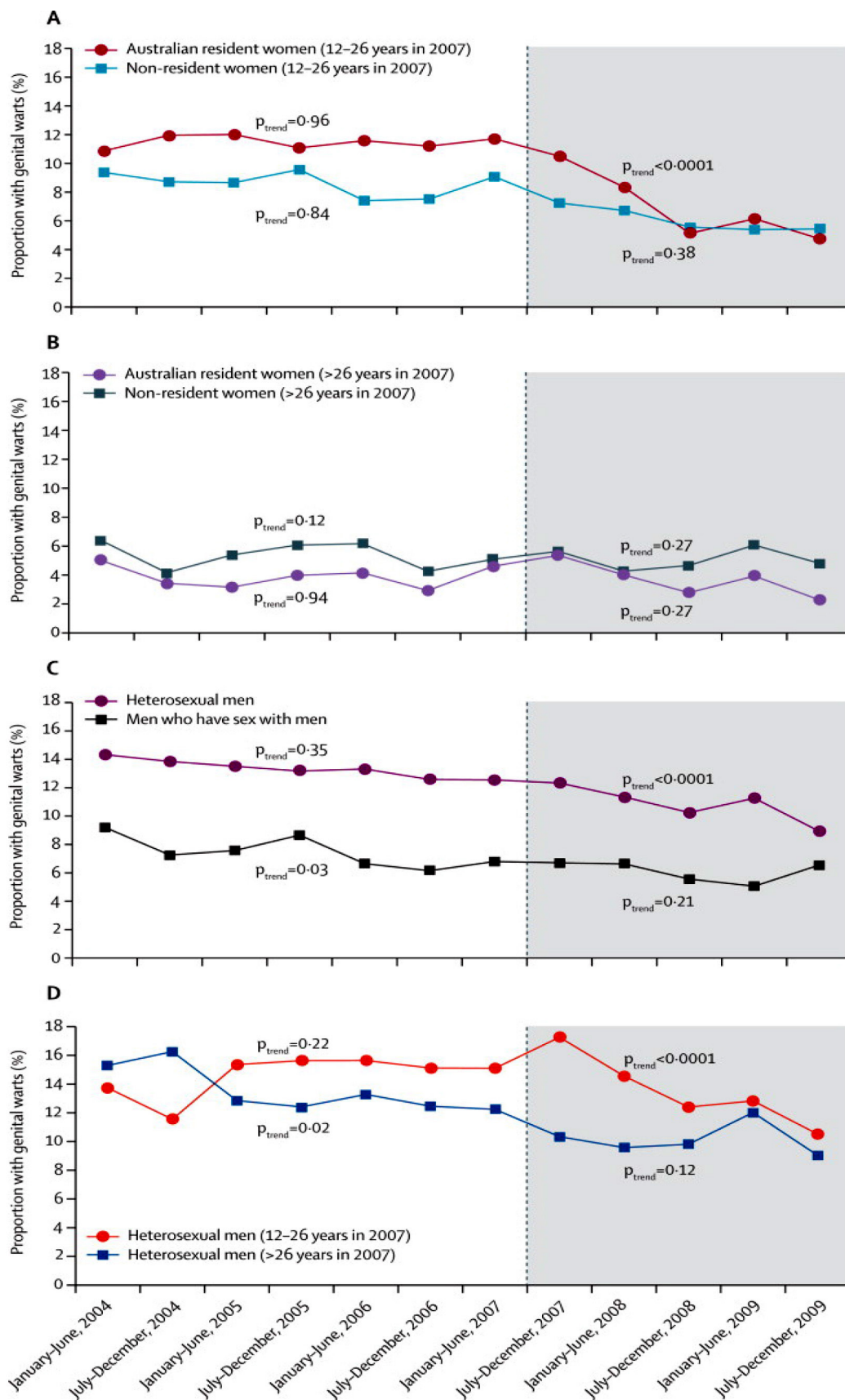


Figure 8. Proportion of people presenting to sexual health services in Australia with genital warts, 2004–09 (6)



The impact of the NZ HPV vaccination programme on the rates of diagnosis at Auckland Sexual Health Service to June 2010 was reported by Oliphant et al. in 2011 (7). A significant decrease in diagnosis of genital warts among the vaccinated cohort was observed to occur between 2007 and 2010. The number of cases and percentages reported in the paper are presented in Table 4.

**Table 4. Number and percentage of first-visit clients diagnosed with genital warts by year and for first six months of 2010 [reprinted with permission (7)]**

Variables	2007	2008	2009	2010 (6 months)
	Number (%)	Number (%)	Number (%)	Number (%)
All	917 (9.2)	897 (7.6)	876 (7.0)	435 (6.6)
Male	491 (9.6)	461 (7.7)	488 (7.8)	241 (7.7)
Female	426 (8.7)	436 (7.6)	388 (6.2)	194 (5.7)
Female > 20 years	292 (7.5)	282 (6.2)	255 (5.4)	152 (5.9)
Female < 20 years	134 (13.7)	154 (12.5)	133 (8.5)	42 (5.1)
Male >20 years	450 (9.5)	413 (7.5)	439 (7.6)	227 (7.7)
Male <20 years	41 (11.5)	48 (10.4)	49 (10.2)	14 (6.9)
Number of clients	9988	11751	12493	6561

### 5.3.3 Herd immunity

The herd immunity provided by HPV vaccination is clearly apparent. The reductions in new cases of genital warts among the unvaccinated sexual partners of the vaccinated population provide evidence for this (refer to section 5.3.2.2 Genital warts). There are two key issues for herd immunity with the current strategy of only vaccinating women:

The issue for MSM who are not deriving any benefit from vaccination programmes that do not include males.

The potential for increasing the impact of herd immunity by vaccinating males where the coverage rates in females are relatively low.

### 5.3.4 Effect on prevalence of infection

The prevalence of HPV-6, -11, -16 and -18 has decreased in Australia since the introduction of HPV4. In the period prior to vaccination (2005–2007), the prevalence was 28.7% among women aged 18 – 24 attending family planning clinics. In the period following vaccine use (2010–2011), the prevalence had dropped to 6.7%. The prevalence of non-vaccine oncogenic types had also reduced from 37.6% to 30.8% (43, 44).

### 5.3.5 Cross protection

Results from two studies assessing cross protection, PATRICIA and FUTURE I and II, indicate generally higher cross protection efficacy from the HPV2 vaccine, however, waning was evident beyond six months. Differences in trial design need to be considered when interpreting these results (Table 5 and Table 6) (45).

As part of the PATRICIA study, the efficacy of HPV2 has been estimated against non-vaccine oncogenic types out to four years. Cross-protective efficacy against persistent infection for HPV-33 (26.3%; 95% CI 8.9 – 40), -31 (46%; 95% CI 37 – 54), -45 (56%; 95% CI 39 – 66) and -51 (14%; 95% CI 3.8 – 22.5) and cervical intraepithelial neoplasia grade two or worse (CIN2+) HPV-31 (47%; 95% CI 20 – 66), -33 (52%; 95% CI 25 – 70), -45 (91%; 95% CI 61 – 99) and -51 (50%; 95% CI 25 – 67) was demonstrated (46).

**Table 5. Efficacy against persistent infection with non-vaccine type human papillomaviruses (adapted from (45))**

	Efficacy against persistent infection (95% CI)	
	HPV2	HPV4
31	77.1% (67.2 – 84.4)	46.2% (15.3 – 66.4)
33	43.1% (19.3 – 60.2)	28.7% (–45.1 – 65.8)
45	79.0% (61.3 – 89.4)	7.8% (–67.0 – 49.3)
52	18.9% (3.2 – 32.2)	18.4% (–20.6 – 45.0)

**Table 6. Efficacy against cervical intraepithelial neoplasia grade two or worse (CIN2+) with non-vaccine type human papillomaviruses (adapted from (45))**

	Efficacy against CIN2+ (95% CI)	
	HPV2	HPV4
31	89.4% (65.5 – 97.9)	70% (32.1 – 88.2)
33	82.3% (53.4 – 94.7)	24.0% (–71.2 – 67.2)
45	100% (41.7 – 100)	–51.9% (–1717.8 – 82.6)
52	30.4% (–45.0 – 67.5)	25.2% (–46.4 – 62.5)

### 5.3.6 Duration of protection

As for many recently licensed vaccines the duration of protection is still unknown. However, there are several indications that protection is likely to be long lasting. There is over eight years of observation of efficacy for HPV2 and five years for HPV4 published with the additional data for HPV-16 monovalent vaccine to eight and a half years. In addition, the geometric mean titre (GMT) plateaux are suggestive of long-term immunity. The patterns and stabilisation of antibody titres are similar to those observed with live attenuated vaccines, with an initial peak in antibody titre occurring shortly after vaccination, followed by a rapid drop and then a sustained plateau. Waning of this plateau is variable, depending on a range of factors, such as the antigen type, age of vaccinee, host and environmental factors. It has been recently proposed that antibody secreting plasma cells may have a predetermined lifespan based on the magnitude of B-cell signalling that occurs during the induction of the original antigen-specific humoral immune response (47).

There is currently no indication that booster doses are required.

### 5.3.7 Vaccine performance in women aged 24 – 45 years

All sexually-active women are at risk for HPV acquisition despite the peak incidence occurring within five – 10 years of the first sexual experience. The efficacy of HPV4 was demonstrated in a randomised placebo controlled trial of 3,819 women aged 24 – 45 years of age. Efficacy against the primary endpoints of disease or infection related to HPV-6, -11, -16 or -18 was 90.5% (95% CI 73.7 – 97.5) in women uninfected at baseline. Efficacy against the second endpoints of disease or infection relating to HPV-16 and -18 only was 30.9% (95% CI 11.1 – 46.5%) and 22.6% (95% CI –2.9 – 41.9), respectively, as infection and disease were present at baseline (48).

### 5.3.8 Vaccine performance in males

The efficacy of HPV4 was evaluated in 4,065 boys and men aged 16 – 26 years from 18 countries in a randomised placebo controlled trial. The efficacy against the primary endpoint of external genital lesions was 60.2% (95% CI 40.8 – 73.8) and 65.5% (95% CI 45.8 – 78.6) for lesions related to vaccine type. In the per protocol population, efficacy against lesions related to vaccine type was 90.4% (95% CI 69.2 – 98.1). Efficacy against persistent infection with vaccine type and detection of related DNA at any time was 47.8% (95% CI 36.0 – 57.6) and 27.1% (95% CI 16.6 – 36.3), respectively, in the intention to treat population and 85.6% (97.5% CI, 73.4 – 92.9) and 44.7% (95% CI 31.5 – 55.6) in the per-protocol population. Among MSM enrolled in the study, there was 94.9% (95% CI 80.4 – 99.4) per-protocol efficacy against anal infection and associated anal intraepithelial neoplasia (AIN) (49).

#### 5.3.8.1 Men who have sex with men

The safety and efficacy of HPV4 against AIN associated with HPV-6, -11, -16, or -18 infections in MSM was evaluated in a randomised trial. The endpoint was prevention of AIN or anal cancer related to infection with HPV-6, -11, -16, or -18. The efficacy against AIN associated with vaccine types was 50.3% (95% CI 25.7 – 67.2) in the intention-to-treat population and 77.5% (95% CI 39.6 – 93.3) in the per-protocol efficacy population. The corresponding efficacies against AIN associated with HPV of any type were 25.7% (95% CI –1.1 – 45.6) and 54.9% (95% CI 8.4 – 79.1), respectively. Rates of AIN per 100 person-years were 17.5 and 13.0 in the intention-to-treat placebo and vaccine groups, respectively, and 8.9 and 4.0 in the placebo group and vaccine per-protocol efficacy population, respectively. The rate

of AIN grades two or three related to infection with HPV-6, -11, -16, or -18 was reduced by 54.2% (95% CI 18.0 – 75.3) in the intention-to-treat population and by 74.9% (95% CI 8.8 – 95.4) in the per-protocol efficacy population. The corresponding risks of persistent anal infection with vaccine types were reduced by 59.4% (95% CI 43.0 – 71.4) and 94.9% (95% CI 80.4 – 99.4), respectively (50).

Men who have sex with men are at higher risk for HPV infection, anal cancer and high-grade anal intraepithelial neoplasia (HGAIN). Among a cohort of 202 MSM patients, with previously treated HGAIN, 88 were vaccinated with HPV4 vaccine. Recurrence of HGAIN was observed in 35 (30.7%) of unvaccinated and 12 (13.6%) of vaccinated patients. In patients infected with oncogenic HPV, vaccination was associated with a decreased risk of recurrent HGAIN at two years after study entry (Hazards ratio 0.47; 95% CI 0.22 – 1.00;  $p=0.05$ ) (51).

## 5.4 Summary of effectiveness

The immunogenicity of both HPV2 and HPV4 has been established to be robust and long-lasting to date. Anamnestic responses have been demonstrated out to 8.5 years. In younger women, two doses appear to be as immunogenic as three doses are in older women; however, the duration of immunity from two doses remains to be established.

Both vaccines are highly efficacious against vaccine-type infection and related outcomes. Some cross protection against non-vaccine oncogenic HPV types has been noted, particularly, for the HPV2 vaccine. In women who have had procedures for pre-existing cervical diseases, there was benefit to receiving vaccination with a reduction in subsequent procedures. Very few women are co-infected with all vaccine types. As the only women who derive no protection from vaccination are those already infected with all vaccine types, there are no benefits to screening prior to vaccination. Vaccination of older women is efficacious.

Modelling the impact of HPV vaccination against cervical cancer supports vaccinating at an early age, prior to sexual debut, and vaccinating males, particularly if coverage of females is relatively low.

As non-vaccine types are responsible for around one third of cervical cancers, the issue of cross protection may be an important one. Data so far suggest that HPV4 offers cross protection against HPV-31 (70%) and some cross protection for HPV-33 and -45 but these numbers are not large enough to reach significance. Greater cross protection appears to be offered by HPV2 against HPV-33, which is the fourth most prevalent type after HPV-16, -18 and -45 (Table 5).

Australia has been using HPV vaccine longer than any other country and vaccine uptake has been relatively high. Between 2007, when vaccination was initiated, and 2010, there has been a profound effect on new cases of genital warts and in Melbourne a near elimination among the vaccinated population and their sexual partners. Other countries have also had a significant reduction in new cases of genital warts, including NZ.

As vaccination programmes have only been in place for a maximum of five years, the duration of protection is not yet known. There is no evidence of waning immunity at this time and no indication for booster doses.

Vaccination of males, including those with HIV infection, has been demonstrated efficacious against HPV-associated cancers and genital warts. There has been reduction in the prevalence of vaccine-type HPV infections noted in Australia, supporting the role of herd immunity.

# 6. Age-specific issues

## 6.1 Objective

The objective of this section is to consider the evidence for offering the vaccine to different age groups, in particular older age groups.

## 6.2 Review

### 6.2.1 Onset of sexual activity

Data from the NZ Youth 2007 survey suggests that over 20% of NZ adolescents may have had sexual intercourse before the age of 13 years. This had increased to nearly 40% by the age of 15 years and over 50% by age 17 years. Rates are higher for Māori. Approximately 15% of sexually active students don't use or only sometimes use a condom (52). Most HPV infections occur within the first two years of onset of sexual activity with more than 40% becoming infected during this period. The first sexual relationship carries a substantial risk (53).

### 6.2.2 Vaccine issues for different age groups

The data from the pivotal studies for both HPV2 and HPV4 have demonstrated potential benefit to women older than 25 years. This is summarised in section 5. Briefly, HPV4 has been shown to be effective at preventing infection and disease from the vaccine types in women aged 24 – 45 years who were uninfected at baseline.

### 6.2.3 Optimal age for vaccination

It is clear that in order to optimise effectiveness, human papillomavirus vaccines need to be administered prior to the acquisition of infection. As the risk for acquiring infection is significant within the first two years of onset of sexual activity, any vaccination programme must target the population prior to this onset.

Modelling in Finland in 2007 was used to explore the optimal age for vaccination and the pattern of vaccine introduction. In the longer term, vaccination during early adolescence, prior to first sexual intercourse, provides the greatest reduction in annual proportion of cervical cancer cases. However, in only vaccinating 12 year olds the decreases in cervical cancer are expected to be delayed when compared with vaccinating older age groups as well. The implementation of catch-up programs (uptake dependent) was predicted to bring forward the time in which a reduction in cervical cancer could be observed, but diminishing returns were seen where the programme was extended beyond six years. It should be noted that the Finnish model assumed an older age for sexual debut than is reported in NZ (54).

## 6.3 Summary of age-specific issues

Human papillomavirus vaccines are highly effective at preventing infection in vaccinees that have not been previously infected with the vaccine types regardless of age. However, given the proportion of adolescents stating they engage in sexual activity prior to 13 years of age, the risk for HPV acquisition for many will be present prior to secondary school.

# 7. Vaccine options

## 7.1 Objective

The objectives for this section are to consider the different vaccine options available for NZ in terms of the available vaccines and schedules.

## 7.2 Review

There are currently two HPV vaccines available internationally.

Modelling has suggested that the use of HPV2 may be associated with a greater reduction in cervical cancer morbidity and mortality, and potentially would offer greater cross protection against non-vaccine oncogenic HPV types; however, it has no impact on genital warts. Costs and quality-adjusted life years (QALY) saved by implementing either vaccine depends on assumptions about the extent of cervical disease caused by the HPV types prevented by cross protection as well as the burden of genital warts caused by HPV-6 and -11 (55).

### 7.2.1 Second generation vaccines

Newer vaccines are being developed to address the limitations of the current vaccines, namely type restriction, high cost of production, and implementation and lack of therapeutic activity.

The only vaccine in phase III studies is Merck's nine-valent vaccine that includes L1 virus-like particles for HPV-6, -11, -16, -18, -31, -33, -45, -52 and -58, which will have the potential to protect against over 90% of cervical cancer. Results were anticipated for 2012 (56).

There is only one published study on a second generation HPV vaccine. This vaccine is delivered to the upper respiratory tract via aerosol. The vaccine induces secretory IgA in the genital tract as well as serum IgG. There has been limited commercial interest in this vaccine and improvement in the delivery system may be required to make this delivery approach a practical alternative to injection (57).

## 7.3 Summary for vaccine options

There are no further vaccine options available at this time. A nine-valent vaccine has completed phase III studies and results are anticipated.

# 8. Options for scheduling

## 8.1 Objective

This section will review the evidence for different options for placement of HPV vaccine on the childhood immunisation schedule and for special groups.

## 8.2 Outcomes

The outcome for which different schedules are compared is immunogenicity. Comments will be made on the efficacy of fewer than three doses measured in the pivotal clinical trials.

## 8.3 Review

### 8.3.1 Number of doses

Both HPV2 and HPV4 vaccines have been assessed for performance using a two-dose regime instead of three doses.

#### 8.3.1.1 HPV2, Cervarix®

The efficacy of HPV2 vaccine in women who received two instead of three doses in a placebo controlled randomised trial was assessed. After four years, the two doses appeared as efficacious as three doses with even a single dose appearing efficacious, although the confidence intervals (CI) were wide for the single dose (27).

In a randomised trial of two formulations of HPV2 (the licensed 20/20F versus 40/40F high-dose antigen), females were stratified by age to receive two doses of either formulation at zero and six months, two doses of 40/40F at zero and two months or three doses of 20/20F at zero, one and six months. The two-dose 20/20F and 40/40F schedules at zero and six months elicited non-inferior immune responses against HPV-16 and -18 to those elicited in the three-dose 20/20F schedule in women aged 15 – 25 years. This was sustained out to 24 months for each of these three schedules. The use of 40/40F high-dose antigen with a shorter dosing interval of zero and two months induced lower titres than the other schedules. It was concluded that a higher antigen formulation was not justified as the currently licensed formulation performed well when given at zero and six months (58).

#### 8.3.1.2 HPV4, Gardasil®

A randomised trial, comparing a two-dose schedule at zero and six months and three-dose schedule at zero, two and six months of HPV4, showed that HPV-16 and -18 antibody responses following the two-dose schedule in adolescent girls were non-inferior to the three-dose schedule in young women one month after the last vaccine dose (31).

### 8.3.2 Alternative schedules

#### 8.3.2.1 HPV2 at varying intervals

In an alternative dosing schedule of HPV2, healthy women aged 15 – 25 years were randomized (1:1) to receive HPV2 vaccine according to the standard dosing schedule of zero, one and six months (n=401) compared with an alternative dosing schedule of zero, one and 12 months (n=403). The outcome was antibody measured at one month after the third dose. Predefined non-inferiority criteria were met one month after the third vaccine dose for both the standard and the alternative schedules. Seroconversion rates for 100% and 100% for HPV-16, and 99.7% and 100% for HPV-18, respectively. Geometric mean titres were 11884.7 and 10311.9 ELISA units/mL for HPV-16 and 4501.3 and 3963.6 ELISA units/mL for HPV-18, respectively (59).

#### 8.3.2.2 HPV4 at varying intervals

HPV4 was assessed in three alternative dosing schedules compared with the standard zero, two and six months. The interventions were: zero, three and nine months; zero, six and 12 months; or zero 12 and 24 months. The outcome was serum antibody titres one month after the third dose. Non-inferiority criteria were met for the alternative schedule groups that received doses at zero, three and nine months (HPV-16 GMT ratio: 0.92 [95% CI, 0.71 – 1.20] and HPV-18 GMT ratio: 0.87 [95%CI, 0.68 – 1.11]) and at zero, six and 12 months (HPV-16 GMT ratio: 0.98 [95%CI, 0.75 – 1.29] and HPV-18 GMT ratio: 0.91 [95% CI, 0.71 – 1.17]). Pre-specified non-inferiority criteria were not met for the alternative schedule group that received doses at zero, 12 and 24 months (HPV-16 GMT ratio: 0.64 [95% CI, 0.48 – 0.84] and HPV-18 GMT ratio: 0.77 [95% CI, 0.62 – 0.96]) (26).



### 8.3.3 Use of human papillomavirus vaccine in males

The US Food and Drug Administration (FDA) licensed HPV4 vaccine for males aged nine – 26 years in 2009 for the prevention of genital warts. Since this time, there has been additional data from the pivotal trials in males to support the use of the vaccine in preventing anal cancer precursor lesions (50).

There have been cost effectiveness studies for vaccinating males. A cost effectiveness study in the US concluded that the vaccination of 12 year old males could be cost effective, particularly if female HPV vaccination remained low. Increasing female coverage (>70%) was seen as a more cost effective strategy in terms of the overall benefit to the population (60).

Another US modelling study evaluated the public health impact of vaccinating a broader age group of males, aged nine to 26 years, with HPV4. They accounted for both the direct and indirect effects of vaccination. It was estimated that vaccinating males, as well as females, would result in the cumulative mean number of cases of genital warts, cervical intraepithelial neoplasia grade 2/3 cases, cancer cases, and cancer deaths by 5,146,000, 708,000, 116,000, and 40,000, respectively, within 100 years. These reductions were found to be cost effective in terms of US dollars and QALYs gained (61).

Based on the direct benefit of HPV vaccination to men, the cost effectiveness data and the relatively low uptake of HPV vaccine in US women, the Advisory Committee on Immunization Practices (ACIP) recommended that all boys 11 to 21 years of age receive HPV vaccination. They also added a permissible recommendation for men 22 to 26 years of age, and MSM and immunocompromised men to 26 years of age (62).

The potential impact of including males in an HPV programme was modelled in Finland. The predicted impact of vaccinating male subjects in addition to female subjects was dependent upon the age of vaccination and the coverage. At younger ages, the number of additional cases prevented is greater. In the long-term, vaccinating males as well as females at 12 or 15 years of age annually prevents an additional 15.1% and 15.5% of cases, respectively (the onset of sexual activity in Finland was assumed significantly older than NZ). If vaccination occurs at age 21, vaccinating male subjects would have very little effect on incidence of cervical cancer, in the long-term preventing an additional 1% of cases, annually.

The benefit of vaccinating both sexes, in terms of the proportion of cervical cancer cases prevented, increased with vaccination coverage, peaking at 50% coverage. If vaccination occurred at age 12, vaccinating male as well as female subjects at 30% or 70% coverage prevents an additional 15% of cases, whereas at 50% coverage an additional 18% of cases may be prevented annually (54).

The HPV4 vaccine has demonstrated high immunogenicity in males aged 9 to 26 years of age and prophylactic efficacy in the older males. The immunogenicity data infers that this efficacy can be extended into the younger age groups. There are currently extension studies evaluating the duration of protection in males.

Persons higher at risk for acquisition of HPV infection identified from the literature include (63):

- Men who have sex with men
- Number of sexual partners (six or more)
- New sexual relationships
- History of miscarriage
- HIV positive

Persons at higher risk for cervical cancer include:

- Early age at first intercourse
- Long time since starting a new sexual relationship
- Cigarette smoking

## 8.4 Summary of schedule options

The current three-dose schedule in NZ vaccinating girls in year eight (approximately 12 years of age) is still strongly supported by the current evidence. However, the relatively early age of sexual debut noted in NZ girls, particularly Māori, may justify moving the age for vaccination earlier, to 11 years (year seven) for example, and co-administration with other vaccines is also supported. The non-inferiority of a two-dose schedule in this younger age group, noted to date, is worthy of consideration and the flexibility of schedules may make programme delivery easier.

Including males in the routine vaccination programme is likely to increase the benefit to the population in terms of HPV related cancer outcomes as genital warts, particularly to MSM who derive no benefit from the current programme.

# 9. Implementation issues

## 9.1 Objective

The objective of this section is to consider the issues around implementation.

## 9.2 Review

One of the key issues for implementation is that of coverage. Modelling has demonstrated that in order to have a significant impact on cervical cancer, high vaccine coverage is required; at least 80% of sexually-naïve females need to be vaccinated to afford a major reduction in cervical cancer rates. Most countries that have introduced HPV vaccination have targeted nine – 14 year old girls with a variety of approaches for catch-ups (64).

There are still some unresolved issues around the duration of protection and whether or not booster vaccinations will be required, and if so, when. Also, regarding cross protection against non-vaccine types, for which some protection has been demonstrated by both vaccines.

Anti-immunisation activities have been an issue for HPV vaccination programmes with misinformation and scare stories prolific on the internet and mainstream media. This has damaged vaccine uptake in some countries (64, 65).

There are two current issues for NZ, in terms of implementation, which could be considered to further optimise the population impact of the HPV immunisation programme:

1. Consideration of moving the school-based programme to year seven or earlier
2. Consideration of including boys in the schedule

The safety and immunogenicity of HPV4 when administered concomitantly with other vaccines, including diphtheria, tetanus, acellular pertussis and inactivated polio (Repevax®) and diphtheria, tetanus and acellular pertussis (Adacel®), in both males and females have been evaluated and found to be well tolerated with no interference with the immune response to either vaccine (17, 18). There are no concerns about co-administration of HPV4 with any other vaccines.

In NZ, the uptake of the funded HPV programme is affected by characteristics of the vaccine recipients and the mix of delivery options (school-based and primary care). The school-based programme has contributed to increased uptake by Māori and Pacific girls who have traditionally had lower immunisation uptakes compared with NZ European. In Auckland in 2009, 71% of 12 year olds were vaccinated with the majority occurring in the school-based programme. The uptake of the first dose of the vaccine series was lowest in decile 10 schools (66%), which have the greatest proportion of students from a high socio-economic background. The provision of HPV vaccinations in a school-based programme resulted in high coverage for Pacific students and improved the equitable coverage for Māori, a primary goal of the HPV immunisation programme. To achieve the targets for vaccination, further investigation into the high decile (and especially single sex) school and European ethnicity is needed. Policy makers may need to consider further strategies to ensure optimal HPV vaccine uptake by all eligible groups (66).

## 9.3 Summary for implementation issues

There do not appear to be any new issues around programme implementation. There are no scientific concerns envisaged, in terms of safety or immunogenicity, if the timing of the HPV programme was moved or boys were included. The flexibility in the administration of doses without impacting on the immunogenicity of either vaccine will be an advantage in any programme. The school-based programme has demonstrated it can reduce social inequities; however, attention may need to be given to the lower uptake among the least deprived.



# 10. International policy and practice

## 10.1 Objective

The objective to this section is to summarise international practice with regard to the use of HPV vaccines.

## 10.2 Review

Recommendations for HPV vaccination vary by country, with the target group for routine vaccination usually in young adolescent girls prior to the onset of sexual activity. This ensures that maximum benefit can be gained from the vaccination programme as well as to the vaccinees. Only HPV4 has been licensed for use in males. The WHO recommends that routine HPV vaccination should be included in national immunisation programmes for girls from age nine through 13 years where possible, sustainable and practical.

### 10.2.1 United States

The HPV vaccine was introduced in the US in 2006 and is usually delivered by primary care providers in the public and private sectors. Coverage with at least one dose among girls aged 13 – 17 years increased from 25% in 2007 to 49% in 2010, with three-dose coverage at 32%. There is a wide variation by state (67). The ACIP recommends routine HPV vaccination for girls at age 11 or 12 years. There is no preference for vaccine. HPV4 was licensed by the US FDA in 2009 for males aged nine – 26 years for protection against genital warts, and in 2010, this was extended to prevention of AIN and anal cancers in both male and females. In 2011, ACIP recommended routine vaccination of males aged 11 or 12 years, for males up to 21 years who have not been vaccinated previously, and for MSM and immunocompromised men up to the age of 26 years (68).

### 10.2.2 European countries

As of 2010, at least 18 European countries had included HPV vaccination into their national schedules.

England has had a HPV vaccination programme since 2008 for girls aged 12 – 13 years. The programme is delivered in schools. Until 2012 the vaccine in use was HPV2, from September 2012 the vaccine was changed to HPV4. In August 2012, the Department of Health placed a call for evidence to support a review of the HPV programme. The issues under consideration were

a two-dose schedule, potential benefits for those not currently offered the vaccine, particularly MSM, and vaccines that protect against a larger number of HPV types.

Scotland offered vaccination from October 2007. A national programme commenced in 2008 and the HPV2 vaccine is routinely offered to all girls aged 12 – 13 years at school. A catch-up campaign was held until 2011 where girls up to 17 years were offered the vaccine.

Ireland has provided the HPV4 vaccine since 2010 and offers it via a school-based programme to girls in the first year of secondary school (aged 12 – 13 years).

### 10.2.3 Australia

Australia was the first country in the world to use an HPV vaccine in a national programme, commencing in 2007, for girls and women up to age 26 years. The HPV4 vaccine has been delivered routinely to girls aged 12 – 13 years via a school-based programme. In 2012, the programme was extended to include boys, aged 12 – 13 years, and a catch-up programme is available to boys aged 14 and 15 years. The school-based delivery of the programme has been successful with over 70% of eligible girls having received three doses of vaccine. Australia is moving their school-based programme from year eight to year seven.

## 10.3 Summary of international policy and practice

HPV programmes have been implemented widely, internationally, since 2007. Uptake of the vaccine varies from country to country.

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