The Immunisation Advisory Centre

Antigen Literature Review for the New Zealand National Immunisation Schedule, 2016:

Human papillomavirus

Prepared as part of a Ministry of Health contract for services by the
Immunisation Advisory Centre
Department of General Practice and Primary Health Care
the University of Auckland

This review is part of a series of antigen reviews commissioned by the Ministry of Health to help inform the National Immunisation Programme.

August 2016

Executive summary

Over 72 countries have human papillomavirus (HPV) vaccine on their National Immunisation Programme. This report summarises new research into HPV vaccines and vaccination published during the past two and half years, from January 2013 to June 2016.

The causal link between human papillomaviruses and cervical cancer was made in the 1980s. Since then, it has been shown that virtually all cervical cancers can 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. HPV types 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. However, clearing an infection does not necessarily lead to immunity and reinfection is possible.

The review covers the recent literature on safety, immunogenicity, efficacy, effectiveness, impact, age specific issues, schedules of quadrivalent and nonavalent HPV vaccines, along with other areas highlighted for review. In the past two years there has been an explosion of research published around HPV vaccines and vaccination. The final library for this review is 1456 with 122 selected for inclusion.

New Zealand epidemiology

There is little New Zealand (NZ) data on the prevalence of HPV infection, however the Dunedin birth cohort study reported that 24.7% of men had antibodies to any of four HPV types (6, 11, 16 or 18) at age 32 years; a likely underestimate of true population prevalence.

Since 2003 the registration rates for cervical cancer have showed a general downward trend. Mortality from cervical cancer has fluctuated during 2003 – 2012. Nearly 20% of deaths from cervical cancer are in Māori females. The registrations for pre-cancers are considerably higher than registrations for cancer and reflect the effectiveness of the cervical screening programme and treatment of these cases. Pre-cancer diagnosis has changed little, however a steady decline can be observed for women 25–34 years of age. The prevalence of HPV-16/18 in confirmed high-grade disease in NZ is comparable to that observed in Australia and Europe. The estimated number of cervical pre-cancers potentially preventable by vaccination is about 2000 in NZ, based on 2012 data.

The incidence rates of squamous cell oropharyngeal cancer in males in NZ have increased rapidly since 2005, with an annual percentage change of 11.9%. In females, rates increased by 2.1% per year since 1982. Incidence rates for oral cavity cancer, which is generally associated with alcohol and tobacco consumption, have remained stable in both sexes since 1982. However, among males, the incidence rate of oropharyngeal cancer now exceeds that of oral cavity cancer in New Zealand.

Genital warts is the most commonly reported viral sexually transmitted infection in NZ. Since 2008, when the vaccine programme commenced, there has been a reduction from 4299 cases to 2003 cases, a decline of 47%.

Safety

HPV vaccines have demonstrated excellent safety profiles. The pivotal clinical trials found no difference in rates of serious adverse events between vaccine and placebo groups. Extensive post-marketing studies to 2012 found no safety signals arose since the vaccines were licensed and a number of large investigations assessed specific outcomes, particularly autoimmune conditions. Post-marketing surveillance systems continue to monitor the safety of HPV vaccination programmes globally.

A summary of the published post-licensure safety data on HPV4 from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults. The review concluded syncope to be associated with the vaccine, and possibly skin infections of which more detailed analysis suggested some were likely injection site reactions. Serious events were carefully examined with no increase in incidence over background rates.

The pivotal clinical trials of HPV9 have found the vaccine to be more reactogenic than HPV4, with injection site reactions and common systemic events (headache, pyrexia, nausea, dizziness and fatigue all slightly higher in the HPV9 groups at rates between 2.3 and 5%, with the exception of headache which occurred in 14.6% of participants. No serious adverse events have been found to be associated with HPV9.

Clinical trial and post licensure data show that both HPV4 and HPV9 are safe in pregnancy. Reports show that the rates of spontaneous abortions, birth defects and other outcomes are comparable to those in the general population. Pregnancy outcomes are similar among HPV9 and HPV4 recipients and similar to the placebo groups from the HPV4 trials and expected ranges reported for pregnant women.

The possible association between HPV vaccine and venous thromboembolism has been extensively investigated using robust methods and large populations and the data do not support a causal association.

This review considered perceived issues around the safety of HPV vaccines that have arisen since 2012. Because infectious agents and molecular mimicry are known triggers for the onset of autoimmune conditions a role for vaccines is biologically plausible. While the large scientific post marketing safety studies have not found any increased risk for autoimmune conditions following exposure to HPV vaccine, concerns about the development of autoimmune diseases after HPV vaccination, based on sporadic case reports, have been fuelled by social and news media.

The possible association between HPV vaccine and multiple sclerosis (MS) has been investigated using robust epidemiological methods with large populations, and although one study found an increased risk in a thirty-day period following vaccination, overall the data do not support a causal association. Similarly, there is no evidence that HPV vaccine increases the risk for systemic lupus erythematosus (SLE).

Two cases of acute disseminated encephalomyelitis (ADEM) occurring at widely different temporal intervals after HPV vaccination were published, do not provide evidence for a causal association. The large post marketing surveillance studies have not detected ADEM as an outcome.

A series of cases of primary ovarian failure with variable temporal onsets months to years later have been published. Empirical studies have not found a safety signal.

Prior to 2014 one case of postural orthostatic tachycardia (POTS) following HPV vaccine had been published in a letter to the European Journal of Neurology. It described a patient developing symptoms two weeks following the first dose of HPV4. Since then many cases have been published, largely by the same authors. A major review by the European Medicines Agency (EMA) that included over 60,000 subjects available for HPV4 found that the incidence of POTS in the HPV4 and HPV9 trials were less than one case per 10,000 person-years and comparable to the placebo cohorts.

Since the EMA review, two important studies have been published that exclude an increased risk for POTS after exposure to HPV vaccine: one clinical trial data included over 15,000 vaccinees, and the other, a cohort of almost quarter of a million girls who had received three doses of vaccine. There was no signal for POTS found in either of these studies.

In addition to POTS, a series of cases of complex regional pain syndrome (CRPS) with variable temporal onsets have also been published. As with the other case reports, empirical studies have not found a safety signal. Among 15,000 clinical trial participants who received HPV vaccine, two subjects were diagnoses with CRPS and both cases were attributed to a previous injury.

Previous studies found coadministration of HPV4 with other vaccines to be safe. Concomitant use of HPV9 has been assessed with tetanus-diphtheria-acellular pertussis (Tdap), Tdap-inactivated poliovirus, measles-mumps-rubella (MMR), hepatitis B and conjugate meningococcal vaccines with no safety concerns.

Immunogenicity

Although there is no known correlate of protection, HPV vaccines generate good antibody responses in most recipients, even those who are moderately immunosuppressed. Two doses are more immunogenic in recipients aged between 9-15 years than older age groups and comparable to three doses in older recipients. A decline in antibody levels is observed within one year of immunisation. In young females, two doses have been found to be non-inferior to three doses, particularly when the interval between doses is more than 4 months. There are some differences between the HPV types and HPV-18 appears to be less immunogenic in some situations, particularly for older women, than the other vaccine-types. Generally, younger recipients have a better response than older adolescents and adults.

Current evidence supports flexibility in the dosing schedules for HPV4 to twelve months post dose one and all data to date supports the coadministration of HPV4 with other vaccines.

Antibody response to HPV4 in men does not differ by age or sexual orientation and is comparable in older men to the response in men under 27 years of age.

Differences in seroconversion rates and antibody titres were seen in immunocompromised individuals. In some cases, differences were seen in antibody response to certain HPV-types. The immune response to HPV4 among immunocompromised children appears adequate. Seroconversion among HIV infected individuals has been demonstrated to be robust and higher among those with lower HIV loads or on antiretroviral therapy. While some immunosuppressive regimes can attenuate the immune response to HPV4, patients with autoimmune diseases generally appear to respond well to the vaccine.

In contrast, older organ transplant recipients produce suboptimal responses to HPV4. Recommendations may include consideration of pre-transplant vaccination or vaccination at a younger age. While some immunosuppression regimes can attenuate the immune response to HPV4 patients with autoimmune diseases generally appear to respond well to the vaccine.

The immunogenicity of investigational HPV9 was initially assessed in an international randomised double-blind phase IIb/III study in women aged 16–26 years. Antibody responses generated by the HPV9 vaccine to HPV-6, -11, -16 and -18 were non-inferior to those generated by the HPV4 vaccine. HPV9 has demonstrated non-inferiority to HPV4 in males and females. Men-who-have-sex-with-men appear to produce lower GMTs than heterosexual men, possibly due to greater exposure to the virus and the phenomenon of original antigenic sin, highlighting the importance of vaccination at a young age.

Efficacy

In pivotal efficacy trials HPV4 demonstrated high efficacy against all endpoints in both males and females, as well as effectiveness in reducing the risk for subsequent HPV related disease. Since the recommendations and widespread introduction of HPV4 placebo-controlled trials are no longer an ethical approach for studying HPV vaccines. The efficacy of HPV9 had to be assessed alongside the HPV4 comparator. Efficacy was assessed in 14,215 women aged 16 to 26 years in a double-blind, phase IIb/III trial. Three doses of either HPV4 or HPV9 occurred at 0, 2 and 6 months. In the per-protocol efficacy population, the incidence rate of high-grade disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-years in the HPV9 group and 1.6 per 1000 person-years in the HPV4 group (1 case vs. 30 cases). HPV9 efficacy was 96.7% (95% CI 80.9 to 99.8).

Effectiveness and Impact

Given the variables that affect the impact of a vaccine programme, the reported impact from different countries varies. What is consistent is the clear positive association between vaccine coverage and impact.

Vaccine effectiveness, and impact, are measured after the implementation of a vaccination programme and, depending on the endpoints being measured, become evident over time. In 2012 there had been four years' practice of HPV vaccine use. In 2016 there has been a further three and a half years of international experience. Since the introduction of HPV vaccination programmes there have been many studies documenting effectiveness and impact: over 130 studies on effectiveness in the period January 2013 to June 2016 have been published.

Successful implementation of HPV vaccination programmes are associated with significant reductions in the prevalence of vaccine-type HPV, particularly among the cohorts eligible for vaccination, their sexual partners, and where coverage is highest. There are no changes observed in groups ineligible for funded HPV vaccine programmes.

In countries with high HPV vaccine coverage, such as Australia and Denmark, there has been a profound reduction in the number of genital wart cases. Data from Australia suggest elimination is possible. Countries with more moderate coverage, such as NZ, have also observed significant reductions.

Declines in cervical dysplasia have now been reported and these are associated with the vaccine eligible cohorts. Data to date support long term effectiveness. Younger women have the strongest evidence of protection after partial doses.

Herd immunity has been observed and is evident for prevalence of infection, incidence of genital warts and cervical disease.

Age specific issues and scheduling

In NZ, 14.2% of youth report the onset of sexual activity has occurred by age 14. Of these 7.8% were aged 13 years or less. This excludes sexual abuse. By the age of 15 years, 24.3% of students have had sexual intercourse. Of those reporting being currently sexually active, 5.6% are aged 13 years or less and 9.6% aged 14 years. To optimise effectiveness, HPV 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.

Conclusions

HPV vaccine is proving highly effective in reducing incidence of persistent infection, genital warts and cervical dysplasia. Where uptake is high the impact is greater with evidence indicating that elimination of genital warts is possible. Extensive data support the safety of these vaccines, however case studies have eroded public confidence in the vaccine programmes.

Contents

Figures and tables

Acknowledgements

The Immunisation Advisory Centre would like to thank Dr Peter Saxton, Senior Research Fellow and Director of Gay Men's Sexual Health research group, Department of Social and Community Health at the University of Auckland for his expertise and feedback for this review.

Abbreviations

ADEM	Acute disseminated encephalomyelitis
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
cLIA	competitive Luminex® immunoassay
DHBs	District health boards
ELISA unit	Enzyme-linked immunosorbent assay unit, a unit of measure for antigen content
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
HepB	Hepatitis B
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)
HSCT	Haematopoietic stem cell transplant
IBD	Inflammatory bowel disease
IRR	Incidence rate ratio
JIA	Juvenile idiopathic arthritis
MCV	Meningococcal conjugate vaccine

MS	Multiple sclerosis
MSM	Men who have sex with men
MCV4	quadrivalent meningococcal conjugate vaccine
MMR	combined measles, mumps and rubella vaccine
n	Number of study participants
NZ	New Zealand
PATRICIA	Papilloma Trial against Cancer In young Adults
POF or POI	Primary ovarian failure or insufficiency
QALYs	Quality-adjusted life years
RCT	Randomised controlled trial
Tdap-IPV	combined tetanus, diphtheria, acellular pertussis and inactivated poliovirus vaccine
SAE	Serious adverse event
STI	Sexually transmitted infection
SHC	Sexual health clinic
SLE	Systemic lupus erythematosus
US	United States
VAERS	Vaccine adverse event reporting system (US)
VSD	Vaccine safety datalink
VTE	Venous thromboembolism
VLP	Virus-like particle
WHO	World Health Organization

Background – disease 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 an 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 causal 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 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.

Between 2007 and 2015 there were 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, and both vaccines offer variable cross-protection against other strains.[2, 3] 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 type-specific 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 9 to 13 years where possible, sustainable and practical.

Since 2009 recommendations have been extended. Currently the American Committee on Immunization Practice recommend routine vaccination with HPV2, HPV4 or HPV9 for girls aged 11-12 and boys 11-12 years to receive HPV4 or HPV9.[4]

The nine valent vaccine, which offers protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, was first licensed in the US in 2014 and in the European Union in 2015.

Vaccination against HPV has the potential to reduce both the incidence of associated cancers and with respect to the HPV4 and HPV9 vaccines, 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 8 (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.

Since implementation of the programme cervical disease and genital warts have continued to decline each year.

1 Methodology for review

1.1 Literature search strategy

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

1. Safety
2. Effectiveness in disease control
3. Implementation issues, with particular reference to practicality of and possible impact on uptake.
4. Differences that need to be considered for each age-group, for example the variable severity of disease and immunisation concerns that differ with age
5. Different option for placement on the schedule, based on international findings and best practice
6. Different vaccine options for each disease and comparison between the options
7. Current international research and evidence around use of vaccines as covered in points 1-6

Other areas of special interest

- Consideration of the high-risk groups and whether the vaccine should be provided to them
- Investigation of the implications for herd immunity
- Investigation of strain shift and suitable vaccines
- Duration of protection provided by vaccines

Medline search terms and strategy

MeSH term: Papillomavirus vaccines

5356

Limit to Human, English, 2013 – current

1704

NOT All Fields: Costs and cost analysis

1699

NOT Keyword heading: parent, physician, survey, interview, attitudes, qualitative

1697

After duplicates removed – 1566

After MeSH term: surveys and questionnaires, and title words OR keywords: cost, financial, parent*, physician*, survey, interview, qualitative, removed – 1302

AND MeSH term: Adverse Effects OR Keyword heading: safety

28

After duplicates removed – 0

AND MeSH term: Effectiveness or Keyword heading: efficacy

5

After duplicates removed – 0

Cochrane Library search terms and strategy

MeSH term: Papillomavirus vaccines, human

Limit to: Cochrane Reviews, Other Reviews, Trials 2013-present

83

After duplicates, MeSH term: surveys and questionnaires, and title words or keywords: cost, financial, parent*, physician*, survey, interview, qualitative, removed – 9

Scopus search terms and strategy

Search term: Human papillomavirus vaccin*

Limit to: Published 2013 – present

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

Exclude Letter, Short survey, editorial

597

After duplicates and title words or keywords: cost, financial, parent*, physician*, survey, interview, qualitative, removed – 93

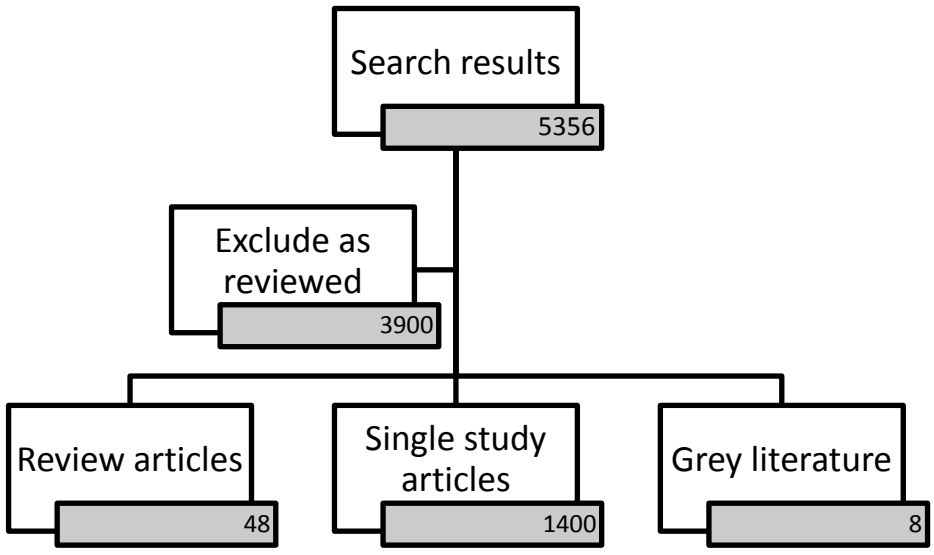
Hand search during review

51

Final Endnote Library 1456 Articles

Where systematic reviews and/or meta-analysis were available the preceding literature has received lower priority for inclusion.

Figure 1. Flow of selection of articles for review



1.2 Participants / populations

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

1.3 Interventions

The interventions included are:

- Quadrivalent human papillomavirus vaccine (HPV4)
- Nonavalent human papillomavirus vaccine (HPV9)

1.3.1 Quadrivalent human papillomavirus vaccine

The licensed HPV4 vaccine (Gardasil®; MSD NZ / Merck and Co, US.) is a recombinant vaccine. The genes for the major capsid protein (L1) of HPV-6, -11, -16 and -18 have been expressed in the yeast *Saccharomyces cerevisiae*. 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-histidine, polysorbate 80, sodium borate and water for injection. Residual yeast protein may be present from the manufacturing process.[5]

1.3.2 Nonavalent human papillomavirus vaccine

Similar to HPV4, HPV9 (Gardasil® 9) is a recombinant vaccine containing purified VLPs of the L1 major capsid protein of HPV-6, -11, -16, -18, with additional L1 proteins of HPV-31, -33, -45, -52 and -58. Each 0.5ml dose contains approximately 30µg, 40µg, 60µg, 40µg of HPV-6, -11, -16, -18, respectively, and 20µg each of HPV-31, -33, -45, -52 and -58 L1 proteins. Each dose also contains aluminium adjuvant (amorphous aluminium hydroxyphosphate sulphate), sodium chloride, L-histidine, polysorbate 80 and sodium borate. Residual traces of yeast protein may be present.[6]

1.4 Study designs

The studies included in this update are meta-analyses, systematic reviews, reviews, randomised controlled trials (RCT), observational studies using database matching, other observational methods and case reports given in Table 1.

Table 1: Number of studies included in this antigen review

Study design	Number included in review
Meta-analysis	5
Systematic review/Cochrane review	9
Review	11
Randomised trial	7
Observational study – data matching (includes cohort, post-hoc analysis, case-control, cross sectional)	10

2 Recent New Zealand epidemiology

2.1 Background

There was clear evidence from 2010 and 2011 data of an impact from the HPV immunisation programme, which was commenced in 2008, on new cases of genital warts in females among the age group targeted for immunisation. As of 2011, there was also evidence of a reduction of genital warts among males aged 15–24 years.[7]

HPV vaccination coverage in NZ has gradually increased since 2008. The nationally-funded programme offered the quadrivalent vaccine to girls in year 8 (aged 12-13 years) in the school based programme, with a catch-up for girls aged up to under 20 years of age. Since that time, the three-dose coverage has gradually increased from 38% in the 1990 birth cohort to 66% for the 2002 birth cohort as of December 2016.[8]

2.2 HPV prevalence

NZ data on the prevalence of HPV infection among New Zealand males and females are scarce. However, the Dunedin birth cohort study reported that 24.7% of men had antibodies to any of four HPV types (6, 11, 16 or 18) at age 32 years, though this is likely to underestimate the true burden of HPV infection.[9]

2.3 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 2012 was published in 2015.[10]

2.3.1 Cervical cancer

In 2012, cervical cancer was the eleventh most common cancer registered for females and the most commonly diagnosed cancer in females aged 25-44 years. The estimated age-standardised incidence rate for cervical cancer was 5.3 per 100,000 women per year.[11] Cervical cancer accounted for 166 cancer registrations in 2012. The registration rate was 2.4 times greater for Māori than non-Māori in 2012; a total of 40 cases occurred in Māori, a rate of 12.6 per 100,000. In 2012, there were 56 deaths from cancer of the cervix, 11 of which were Māori.[10] Since 2003 the registration rates for cervical cancer have showed a general downward trend, as shown in Figure 2.

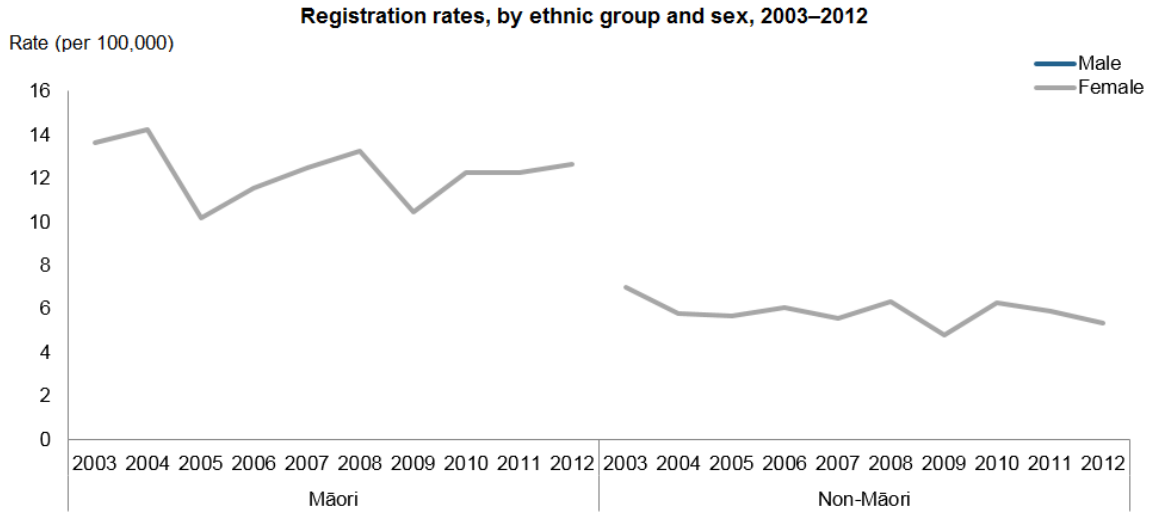


Figure 2. Registration rates of cervical cancer rates, 2003 – 2012 (source: Ministry of Health)

Mortality from cervical cancer has fluctuated during 2003 – 2012 (Figure 3). Nearly 20% of deaths from cervical cancer are in Māori females.

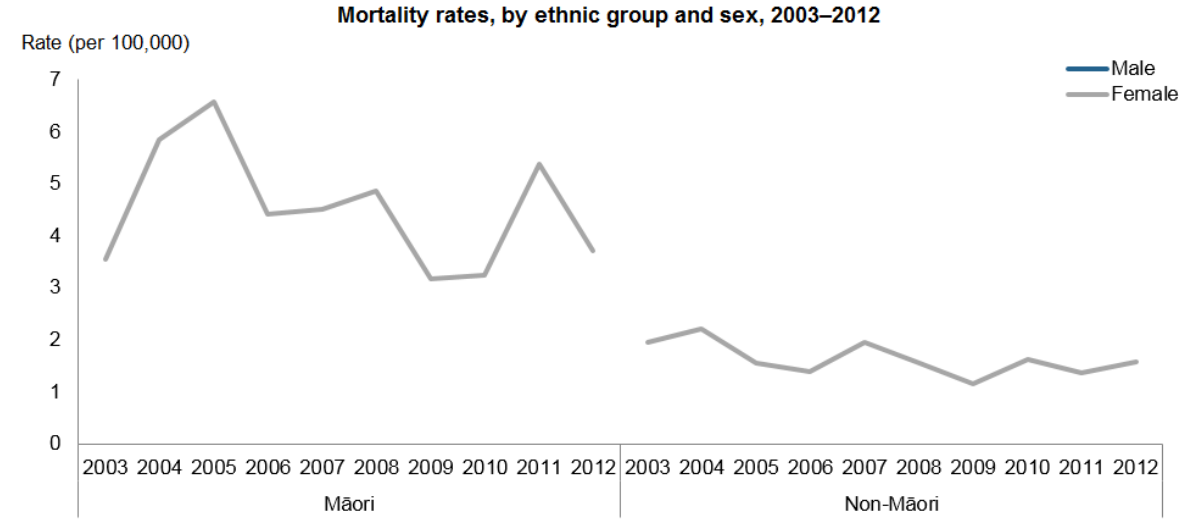
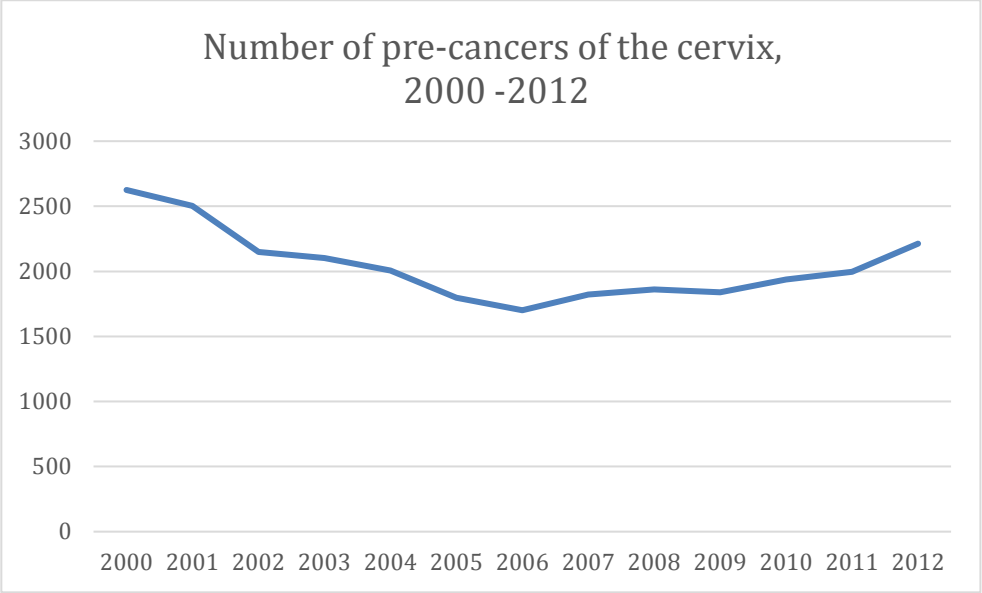


Figure 3. Mortality rates for cervical cancer 2003 – 2012 (source: Ministry of Health)

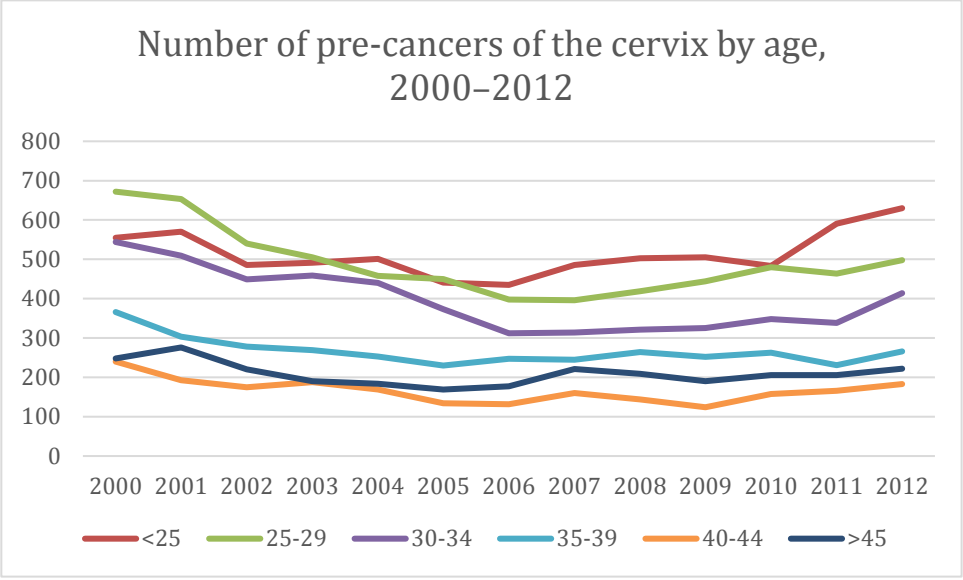
While the overall numbers of cervical cancer registrations are relatively small, the registrations for pre-cancers are considerably higher and reflect the effectiveness of the cervical screening programme and treatment of these cases. The number of pre-cancers of the cervix, which include CIN3 and carcinoma in situ, have fluctuated during the 2000 to 2012 period. There were 2213 registrations for pre-cancer of the cervix in 2012. The year with the lowest recorded registrations of 1701 was 2006 and that with the highest was 2000 when 2625 pre-cancers were registered (Figure 4).[12]

Figure 4. Number of pre-cancers of the cervix, 2000 – 2012; includes CIN3 (cervical intraepithelial neoplasia grade 3) and carcinoma in situ. (Source: Ministry of Health)



Cervical disease is more commonly diagnosed in younger women. While there has been little change over time in registrations for women 35 years of age and a steady decline can be observed for women 25 – 34 years of age. As shown in Figure 5, in the youngest age group numbers have increased.[12]

Figure 5. Number of pre-cancers of the cervix by age, 2000–2012. (Source: Ministry of Health)



A cross-sectional study conducted in NZ investigated the distribution of high-risk and low-risk HPV in 227 cervical specimens collected from women during 2004 and 2010 diagnosed with invasive cervical cancer (ICC) stage 1b or greater. HPV infection was detected in 88.5% of ICC samples and 87.2% were high-risk types. Single type infections were seen in 93.5% of women compared with 5.5% with multiple infections. The most commonly detected high-risk types were HPV-16 (51.1%), HPV-18 (20.7%), HPV-31 (4.0%), HPV-45 and HPV-52 (both 3.1%). HPV type distribution was similar between Māori and non-Māori women, overall.[13]

The prevalence of oncogenic HPV infection in women aged 20-69 years with high-grade cervical abnormalities, including CIN2/3 or cytology predicting high-grade dysplasia, were measured. The study found that the most common HPV types were 16, 52, 31, 33 and 18 (51%, 19%, 17%, 33%, and 12%, respectively). The prevalence of HPV-16/18 in confirmed high-grade disease in NZ was comparable to that observed in Australia and Europe. The test-positive rate of type-52 appears higher in NZ than other developed countries.[14]

2.3.2 Vulvar and vaginal cancer

In 2012, there were 67 new registrations for cancer of the vulva and 14 for cancer of the vagina. An international study detected HPV DNA in 28.6% of vulvar, 74.3% of vaginal cancer specimens and in 86.7% and 95.8% of high-grade neoplasia (VIN 2/3 and VaIN2/3, respectively). HPV-16 was the most frequent type in all anogenital lesions in women. Worldwide the relative contribution of nine HPV types (16/18/31/33/45/52/58/6/11) was 87.1% in invasive vulvar cancer, 94.1% in VIN2/3, 85.5% of vaginal cancer and 78.7% of VaIN2/3.[15]

2.3.3 Penile cancer

There were 15 registration for cancer of the penis in 2012, one case occurred in a Māori man, and there were two deaths from cancer of the penis.[10] Penile cancer is also rare, with an estimated age-standardised incidence rate of 0.4 per 100,000 males per year in New Zealand from 2003-2007.[11]

2.3.4 Anal cancer

A total of 72 cases of cancer of the anus were registered in 2012; 20 in males and 52 in females. Six cases occurred in Māori. In 2012 there were 20 deaths from cancer of the anus. Compared with cervical cancer, a greater proportion with anal cancer died in 2012 (around 1 in 3.5 versus 1 in 2.5) demonstrating that the burden of anal cancer is relatively high.[10]

Anal cancer remains comparatively rare, when compared to other cancers, but the global incidence has increased among both men and women, particularly in developed regions. In NZ, during the period of 2003-2007, the age-standardised rate for anal cancer was 0.5 and 1.1 per 100,000 persons per year among men and women in New Zealand, respectively.[11]

Internationally, men-who-have-sex-with-men (MSM) have been shown to carry the burden of HPV-related anal cancers. A meta-analysis estimated the incidence of anal cancer among HIV-negative MSM to be 5.1 per 100,000 persons per year; among HIV-positive MSM the estimate was 77.8 per 100,000 persons per year.[16] However, in New Zealand data on sexual orientation is not available on the National Cancer Registry and so the burden among sexual orientation minorities cannot be estimated.

2.3.5 Oral cancers

Several oral cancers are associated with HPV, predominantly HPV-16. Primarily, these are located in the posterior regions of the oropharynx, which includes the base of the tongue, back of the throat, tonsils, tonsillar crypts and tonsillar pillars. In 2012 there were 30 registrations for cancer of the base of the tongue (25 male, 14 female); 66 registrations for cancer of the tonsil (52 in males, 14 in females); 13 cancers of the oropharynx (10 male, 3 female); 15 registrations for cancer of the palate (7 males, 8 females). Oropharyngeal cancer age-standardised incidence in New Zealand for 2012

was estimated to be 2.4 per 100,000 males per year among men and 0.4 per 100,000 females per year.[11]

A recent study found the incidence rates of squamous cell oropharyngeal cancer in males in NZ to have increased rapidly since 2005, with an annual percentage change of 11.9%. In females, rates increased by 2.1% per year since 1982.[17]

Incidence rates for oral cavity cancer, which is generally associated with alcohol and tobacco consumption, have remained stable in both sexes since 1982.[17] Among males, the incidence rate of oropharyngeal cancer now exceeds that of oral cavity cancer in New Zealand.

2.3.6 Potential cancers and pre-cancers prevented

Based on the estimates of proportions of cancers associated with HPV and on cancer registry data for 2012, Table 2 summarises numbers of cases potentially preventable in 2012 by HPV9.

Table 2. Number of incident cancers and pre-cancers in New Zealand in 2012 potentially preventable by vaccination

	Women (n)	Men (n)	% of cases associated with HPV	% of HPV associated cases due to HPV-16,18,31,33,45,52 & 58	Cases potentially preventable by vaccination in 2012	
					Women (n)	Men (n)
Cervical cancer	166	-	100%	90%	149	-
Cervical pre-cancer	2213		100%	90%	1992	-
Vulvar cancer	67	-	40%	86%	23	-
Vaginal cancer	14	-	70%	88%	9	-
Penile cancer	-	15	50%	87%	-	7
Anal cancer	52	20	85%	93%	41	14
Cancer of the base of tongue and oropharynx	35	8	66%	94%	22	5
Total	**2547**	**43**			**2236**	**26**

2.4 Genital warts

2.4.1 National trends

Genital warts are the most commonly reported vital STI in NZ. Most reporting comes from Sexual Health Clinics (SHC) throughout 19 district health boards (DHBs) with additional reporting coming from Family Planning Clinics (FPC). Reporting represents a significant underestimation as it does not include all other avenues for presentation, particularly at general practice. However, the total number of clinic visits for each type of centre has remained relatively stable over the past 14 years, with the exception of student and youth health clinics, where usage has increased since 2005. This is attributed to the addition of clinics at Victoria University of Wellington and the University of Otago.

In 2014 there were 2003 first presentation cases of genital warts reported by SHCs and FPC, a decrease by 4.2% and 8.9% respectively since 2013. Since 2008, when the vaccine programme commenced, there has been a reduction from 4299 cases to 2003 cases, a decline of 47% as illustrated in Figure 6.[18] Decreases in number of new cases of genital warts in women under 20 years of age were already being observed by Auckland Sexual Health Service in 2010.[19]

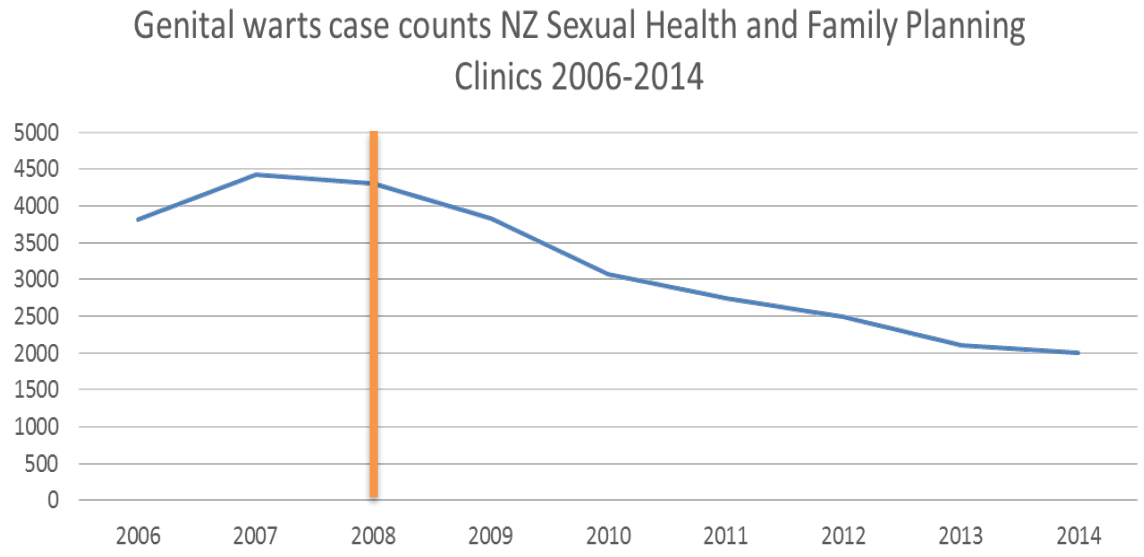


Figure 6. Genital warts case counts NZ Sexual Health and Family Planning Clinics 2006-2014 (Data source: ESR)

2.4.2 Regional trends

The highest numbers of genital warts cases in SHCs are seen in the Auckland and Wellington regions, followed by Waikato and Canterbury (Table 3). The decrease in genital warts nationally is reflected in the trends across all DHBs over the post vaccine period.

DHB	Clinic type		Total
	SHC	FPC	
Northland	41	10	51
Auckland region [a]	635	58	693
Waikato	175	23	198
Lakes	29	0	29
Bay of Plenty	168	4	172
Tairawhiti	0	9	9
Taranaki	71	1	72
Hawkes Bay	48	0	48
Whanganui	5	5	10
MidCentral	37	0	37
Wellington region [b]	195	38	233
Nelson Marlborough	66	8	74
West Coast	11	1	12
Canterbury	174	38	212
South Canterbury	12	1	13
Southern	110	30	140

[a] Waitemata, Auckland and Counties Manukau
[b] Hutt Valley and Capital & Coast

Table 3. Genital warts (first presentation) case numbers by clinic type and DHB, 2014 (Source: ESR)

2.4.3 Distribution by gender

There are more cases of genital warts seen in males than females in the SHC setting (61%), whereas in the FPC context 70% of cases are in female visitors, reflecting the sex distribution in FPCs where the male to female ratio is 1:23.

2.4.4 Distribution by age

The age group with the highest number of genital warts cases is 20–24 years for both males and females. However between 2010 and 2014, the number of cases decreased markedly in the 15-19 and 20-24-year age groups and a modest decrease in cases were observed in the 25-29-year age group, for both males and females. In SHC, 39% reported cases were seen in those younger than 25 years, and a higher proportion (62.4%) of under 25-year olds were seen in FPCs than SHCs. The mean age of cases were in SHCs and FPCs were 29.5 years and 24.2 years, respectively.[20]

2.4.5 Distribution by ethnicity

Of the 1734 genital warts cases reported at SHCs during 2014, for which ethnicity was recorded, 69.4% had European ethnicity, 13.8% Māori, 13.1% Other and 3.7% Pacific peoples. Ethnicity was recorded for 217 cases in FPCs, of which 70.5% had European, 18.9% Māori, 5.5% Other and 5.1% Pacific ethnicities. During 2010-2014, decreases in cases were observed for all ethnicities, except for the Other ethnic group diagnosed in SHCs.[20]

2.5 Summary epidemiology

The overall burden of HPV infection in NZ is unknown, however as shown by the 2012 data, there has been significant impact on burden from cervical cancer. Almost all cases of cervical cancer are associated with HPV infection and it is the most commonly diagnosed type of cancer in women aged 25-44 years; the rate in Māori women was 2.4 times higher than in non-Māori women. As of 2012, registrations for pre-cancer cases were considerably higher than cancer cases, demonstrating the effectiveness of the cervical screening programme. A decline in pre-cancer cervical disease has been observed for women aged 25-34 years, however, numbers have increased in women younger than 25 years.

There were 20 anal cancer and two penile cancer deaths in 2012. The burden in different sexual orientation groups is not recorded.

Several oropharyngeal cancers are primarily associated with HPV-16. Annual rates of squamous cell oropharyngeal cancer have risen rapidly in males by 11.9% since 2005 compared with 2.1% since 1982 in females. Oral cavity cancer rates, which are associated with tobacco and alcohol not HPV infection, have remained stable since 1982.

Based on 2012 data HPV vaccination has the potential to prevent over 2000 cases of cervical cancer and pre-cancers. HPV is associated with 86-93% of anogenital cancers in males and females and vaccination potentially could have prevented 23 cases of anal cancer and vulvar cancer in women in 2012. The greatest burden of oropharyngeal cancer is seen in males, 94% of which are associated with HPV types in the current vaccines.

Since the commencement in 2008 of the HPV vaccination programme in females, the number of genital warts cases in NZ has declined by 47% across in all regions. The greatest decreases have been seen in the 15-19 years and 20-24 years age groups for both males and females, indicating that immunisation is providing herd immunity to subgroups of unvaccinated males. The reported incidence is highest in those with European ethnicity, likely reflecting the visitors to SHCs.

3 Safety

3.1 Background

HPV vaccines have demonstrated excellent safety profiles. The pivotal clinical trials found no difference in rates of serious adverse events between vaccine and placebo groups. Extensive post-marketing studies to 2012 found no safety signals raised since the vaccines were licensed and a number of large investigations assessed specific outcomes, particularly autoimmune conditions. Post-marketing surveillance systems globally continue to monitor the safety of HPV vaccination programmes.

The post-licensure safety has been monitored by the vaccine manufacture, public health authorities, regulatory agencies as well as academics using a range of epidemiological tools and include both passive and active studies.

Safety was reviewed in the 2012 antigen review.[21] The review at the time concluded that both HPV2 and HPV4 vaccines had excellent safety profiles. No safety signals had been raised since the vaccines were licensed and a number of large investigations had been carried out to assess specific outcomes, particularly autoimmune conditions.

Case reports of AEFI following HPV vaccination have also been published, and while these serve to generate hypothesis for testing they do not contribute to evidence as to a causal relationship. However, since 2012 such case reports have resulted in a loss of confidence in HPV vaccination programmes in many countries. In 2015 the European Medicines Agency (EMA) began an investigation into HPV vaccine and complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) to address the public concerns. This review includes evidence and discussion about these perceived safety issues as well.

With respect to the assignment of causality to adverse events following immunisation (AEFI), the US Vaccine Safety Committee at the Institute of Medicine pose three questions in their report on Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality, as listed below, and these serve as a useful framework in which to consider specific events.[22]

1. Can it? This question pertains to the potential for causality. Can the vaccine cause the adverse event, at least in certain people under certain circumstances?
2. Did it? In an individual who has received the vaccine and developed the adverse event, was the event caused by the vaccine?
3. Will it? Will the next person who receives the vaccine experience the adverse event because of the vaccine OR, how frequently will vaccine recipients experience the adverse event as a result of the vaccine?

Each of these questions requires different approaches for assessment. It is important to note that case reports cannot answer any of them and serve only for the generation of hypotheses. This frame work will be referred to in discussion of events that have limited empirical evidence.

3.2 Objective

The objective of this section is to review the most recent safety data for currently licensed HPV vaccines. Only AEFI that have been considered subsequent to the pivotal

clinical efficacy trials will be reviewed here, and any important clinical differences between HPV4 and HPV9. Also considered are the perceived issues around the safety of HPV vaccines that have arisen since the 2012 review.

3.3 Outcomes

Outcomes are 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.

3.4 Review

3.4.1 Safety of quadrivalent human papillomavirus vaccine

There have been extensive post-licensure studies conducted to monitor the safety of HPV4. The previous antigen review in 2012 concluded that there were no new safety concerns with regard to HPV4 since the pivotal clinical trials. Vaccination was associated with same-day syncope and skin infections within two weeks of vaccination. However, reported skin-associated events were noted likely to have been injection site reactions rather than infections.[21]

A summary of the published post-licensure safety data on HPV4 from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults. The review concluded syncope to be associated with the vaccine, and possibly skin infections of which more detailed analysis suggested some were likely injection site reactions. Serious events were carefully examined with no increase in incidence over background rates.[23]

The largest studies to examine the safety of HPV4 are the register-based studies in Denmark and Sweden which include a cohort of 997,585 girls aged 10-17 of whom 30% had been vaccinated with 696,420 doses of vaccine. The studies have evaluated a total of 53 pre-specified conditions, which include autoimmune, neurologic and venous thromboembolism. Incident of hospital diagnosed disease was captured for up to 180 days after each HPV4 dose. There was no association between exposure to HPV4 and the 53 pre-specified events.[24]

3.4.2 Safety of HPV4 and HPV9 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 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.

3.4.2.1 Safety of HPV9 in pregnancy

During the seven phase III studies of HPV9, pregnancies occurred in 2950 of the more than 15,000 subjects after the initiation of the study. Pregnancies were followed to outcome and serious AEFIs occurring in the infants were collected throughout the study.

Pregnancy outcomes were similar among HPV9 and HPV4 recipients, similar to the placebo groups from the HPV4 trials and within expected ranges reported for pregnant women.[25]

3.4.3 Specific events

3.4.3.1 Venous thromboembolism

Venous thromboembolism (VTE) is the formation of blood clots in the vein. There are range of acquired risk factors which include pregnancy, oral contraceptives, inflammatory diseases including some autoimmune diseases, obesity and infection.

Following a disproportionately high reporting of VTE following vaccination in 2009 to the vaccine adverse event reporting system (VAERS) database in the US, sequential analysis of the Vaccine Safety Datalink (VSD) in 2011 highlighted that further study was required.[26, 27] The Scandinavian registers have been used to conduct observational studies to test this hypothesis.

A register-based cohort study using the Danish and Swedish registers between 2006 and 2010 (Arnheim-Dahlström et al, 2013) included 997,585 girls aged 10-17 of who 296,826 had received 696,420 doses of HPV4. There was no association between exposure to HPV4 and venous thromboembolism (rate ratio 0.86, 95% CI 0.55-1.36).[24]

A larger 2006 to 2013 cohort was evaluated using the Danish register for a self-controlled case series study to examine the VTE association was published in 2014. From a source population of 1,613,798 women that included 500,345 (31%) who had received HPV4, there were 4375 incident cases of VTE. Of these, 889 women (20%) were vaccinated during the study period. No association between the HPV4 and VTE during the 42 days following vaccination was found and no association between HPV4 and VTE in subgroup analyses.[28]

A 2014 evaluation of the Canadian passive AEFI reporting system from 2007 to 2011 found 133 AEFIs reported following the distribution of 691,994 doses of HPV4. There were no VTE events reported.[29]

A more recent study in 2016, using the VSD datasets and a self-controlled cases series method in young adults aged 9-26 years, identified cases who had been vaccinated with at least one dose of HPV4 and confirmed the diagnosis by reviewing medical records. The risk within the 1-60 day period following vaccination was calculated and stratified by age, gender, hormonal contraceptive use and recent surgery or trauma. Of the 156 cases with sufficient medical records, 97% had at least one known risk factor for VTE. Only three cases were in males. The risk of VTE varied from 1.47 (0.47–4.64) in the 1–7 days following HPV4 exposure to 0.92 (0.54–1.57) in the 1–60 days following vaccination. There was no elevated risk for developing VTE following HPV4 exposure.[30]

The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program is a safety monitoring component of the US FDA Mini-sentinel project that uses electronic information. This system was used in 2016 to evaluate the risk of VTE following HPV4 among 9-26 year old females and also consider the effect of combined hormonal contraceptives as a confounder or effect modifier. There were 279 potential VTE cases identified following the administration of 1,423,399 doses of HPV4, 225 had obtainable medical records, and 53 were confirmed first-ever VTE. All 30 cases with onsets in risk or control intervals had known risk factors for VTE. VTE risk was not elevated in the first 7

or 28 days following any dose of HPV in any analysis. There was no clustering of VTE onsets after any dose.[31]

The only two studies to report an increased risk of VTE following HPV4 vaccination are based on either a passive reporting system[26] or very few cases with known risk factors. Follow up studies with fewer limitations have consistently found no association.

The possible association between HPV vaccine and VTE has been investigated using robust methods and large populations and the data do not support a causal association.

3.4.4 Autoimmunity

An autoimmune disease, more recently termed immune-mediated inflammatory disease, is caused by an immune response against healthy tissue. Many triggers to an autoimmune response that have been identified, however, while many risk factors have been identified, the exact cause is not known. A range of autoimmune conditions exist and some are more common than others. Because infectious agents and molecular mimicry are known triggers for the onset of autoimmune conditions a role for vaccines is biologically plausible.

3.4.4.1 Multiple Sclerosis

Pellegrino et al (2013) assessed the relationship between HPV vaccination and multiple sclerosis (MS) by analysing VAERS, the EMA and the Australian adverse event databases. They found similar incidence of reports from all databases and concluded that the temporal relationship between HPV vaccination and symptom onset did not provide evidence for a causal relationship and that their results raised questions about a possible relationship.[32] Their subsequent evaluation of US hospitalisations, including emergency department visits, for systemic lupus erythematosus (SLE) found no increase in the age group exposed to HPV vaccine.[33]

A 2014 US based nested case-control study by Langer-Gould et al, using the Kaiser Permanente Southern California Health Management Organisation, evaluated hepatitis B and HPV vaccines and central nervous system demyelinating diseases. Cases were MS or other acquired central nervous system demyelinating syndromes. Out of the 780 incidence cases and 3885 controls were identified, 92 cases and 459 controls were in females aged 9 to 26 years. There were no associations between HPV vaccine (or hepatitis B vaccine) and the risk of central nervous system demyelinating disorders, including MS, up to three years post vaccination. However this study identified an increased risk of vaccination of any type and onset these disorders within 30-days, supporting a possible relationship in the acceleration from subclinical to overt disease in patients with existing disease.[34]

To investigate a possible link between HPV vaccination and demyelinating diseases Scheller *et al* (2015), used the Danish and Swedish registers to perform a cohort study. The study cohort included all females aged 10 – 44 years followed from 2006 to 2013. Two analyses were conducted, one using a cohort design and another analysis using a self-controlled cases-series. The risk period was two years following vaccination. A total of almost four million females of whom 789,082 received almost two million doses of HPV4 vaccine were assessed. There were almost 8,000 cases of demyelinating diseases, and of these, 73 cases of MS and 90 cases of other demyelinating diseases occurred during the risk period. No increase in risk was shown in vaccinated persons. In the self-controlled study there was also no increased risk.[35] These findings, using a larger

population and two methodological approaches, including a cohort design, do not support those of the Langer-Gould study.

The evidence related to HPV vaccine and MS was reviewed by the WHO's Global Advisory Committee on Vaccine Safety, which concluded that while serious adverse events have been reported these have been investigated and not confirmed. While surveillance data and epidemiological studies monitoring the safety of HPV vaccine offer reassurance, allegations of a link to autoimmune diseases continue to surface in the media.[24]

The possible association between HPV vaccine and MS has been investigated using robust epidemiological methods with large populations and although one study found an increased risk in a 30-day period following vaccination, overall the data do not support a causal association.

3.4.4.2 Other autoimmune diseases

The Arnheim-Dahlstrom 2013 study, using the Danish and Swedish registry data, measured incident hospital-diagnosed autoimmune outcomes for up to 180 days after each HPV4 dose. There was no evidence in this large cohort study to suggest HPV4 vaccine is associated with autoimmunity.[24]

A European study (Grimaldi-Bensouda, 2014) investigated the association between HPV4 and the change in risk for autoimmune disorders in a systematic case-control study of incidence cases across France. Cases from 113 participating centres were reviewed. The conditions were idiopathic thrombocytopenic purpura (ITP), MS, Guillain–Barré syndrome, connective tissue disorders (SLE, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus and autoimmune thyroiditis. Matched controls came from general practice. No increase in the risk of the selected autoimmune conditions as a group was found, and there were too few cases of the individual conditions for statistical power.[36]

Geier and Geier (2015) conducted a case-control study using the VAERS database.[37] They selected cases of specific autoimmune events and the controls were formed by the balance of VAERS reports in females. They concluded that the selected conditions were more likely in women exposed to the HPV4 vaccine. Because the VAERS is an uncontrolled, non-systematic database, it is not possible to either obtain controls from this source or to assign causality. The Centers for Disease Control and Prevention and US FDA, who sponsor the VAERS database, make clear the data cannot be used for establishing cause and effect relationships. Therefore the findings and conclusions from this study are meaningless.

While the large scientific post-marketing safety studies have not found any increased risk for autoimmune conditions following exposure to HPV vaccine, concerns about the development of autoimmune diseases after HPV vaccination, based on sporadic case reports, have been fuelled by social and news media.

3.4.4.3 Case reports 2013 – 2016: Systemic lupus erythematosus

In 2013 Gatto et al reported on six cases of SLE or SLE-like disease in temporal association with HPV vaccination. All of the patients had either a personal or a familial history of autoimmunity. The authors concluded that autoimmunity could be exacerbated by HPV vaccination. However these cases did not appear in a consistent temporal association with vaccination and occurred after first, second or third dose.[38]

Can it? Vaccines are biologically active products, therefore it is biologically possible for them to trigger an autoimmune response.

Did it? In order for a direct causal association, cases should appear in a cluster in temporal association. The cases were reported by Gatto to have occurred 5 days post dose three, 3 weeks post dose two, 8 days post dose one, 3 weeks post dose two, and a flare up 10 days post dose two. While these cases are hypothesis generating there is no evidence to suggest that these cases are not coincidentally associated.

Will it? SLE is an anticipated AEFI, particularly in young women in whom the risk of onset is highest. The large aforementioned post-marketing surveillance studies have included SLE as an outcome and consistently concluded there is no increased risk of onset among vaccinated women.

Conclusion. There is no evidence that HPV vaccine increases the risk for SLE. (Note, one of the senior authors, Yehuda Shoenfeld, has published other similar case reports and has had more than one paper retracted based on scientific merit and conflicts of interest.[39]

3.4.4.4 Case reports 2013 – 2016: Acute disseminated encephalomyelitis

Although uncommon, acute disseminated encephalomyelitis (ADEM) is usually preceded by an infection, although in some cases immunisation has been noted as the only preceding risk. In 2014 Pellegrino *et al* published their observations of two cases of ADEM, one 6 months and the other 15 days after HPV vaccination.[40]

Can it? Vaccines are biologically active products, therefore it is biologically possible for them to trigger an autoimmune response. ADEM has been documented to occur after vaccination.

Did it? In order for a direct causal association cases should appear in a cluster in temporal association. These two cases occurred at 15 days and 6 months providing no temporal pattern.

Will it? ADEM is an anticipated AEFI following vaccination. The large aforementioned post marketing surveillance studies have not detected ADEM as an outcome.

Conclusion: Two cases occurring at widely different temporal intervals after HPV vaccination do not provide evidence for a causal association.

3.4.4.5 Case reports 2013 – 2016: Primary Ovarian failure / insufficiency

The first single case of primary ovarian insufficiency (POI) reported in association with HPV vaccine was published in 2012 by Little et al with a two further cases following reported in 2014 by the same authors.[41, 42] The first case experienced symptoms some undisclosed months (>5) after the third dose of vaccine. The second case was experienced 'about' a year after the third dose and the third case after the first menstrual period following the third dose.[42]

In 2013 a series of three cases was published by Colafrancesco et al.[43] These six cases were then reviewed in a 2015 paper by Gruber and Shoenfeld,[44] who do not note the time to onset of POI, which for most of the cases is inconsistent and more than a few months following the third dose. The authors associated the cases with a syndrome proposed by one of the senior authors, Yehuda Shoenfeld, called autoimmune/inflammatory syndrome induced by adjuvants (ASIA) or Shoenfeld's Syndrome.[43]

Pellegrino et al. attempted to assess a potential association between primary ovarian failure (POF) and HPV vaccine using passive reporting data with the denominator derived

from an estimate of doses delivered. They assessed the reporting rates from the US, European and Australian passive reporting systems and found seven cases. They also evaluated the hospital discharges. Neither assessment revealed an increase in POF among the population exposed to HPV vaccine.[45] However the use of passive reporting data to assess causality is not appropriate as spontaneous reporting is based on signal generating and vaccine exposure cannot be assigned. The hospitalisation data is less prone to reporting bias. While these authors did not find an association, this evidence is weak at best.

Can it? While an autoimmune response is biologically possible and a syndrome "ASIA" has been proposed, the hypothesis has not been accepted by the scientific community and no scientific evidence exists as to its validity. Among all the post-licensure studies of vaccines no evidence exists to support an association between these routinely used aluminium adjuvant containing vaccines and autoimmunity.

Did it? The cases thus far described are ill-defined and do not have consistent temporal onsets and most occur many months, sometimes years later.

Will it? There is no evidence to support a link between POI/POF and HPV4 vaccine in the literature. In contrast, the pivotal clinical trials found no difference in the pregnancy rate between vaccinated and placebo groups.

Conclusion: Cases occurring at widely different temporal intervals after HPV vaccination do not provide evidence for a causal association and empirical studies have not found a signal.

3.4.4.6 Case reports 2013 - 2016: Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) is a condition in which tachycardia occurs when a patient moves from a supine position to upright. The condition is associated with collection of other symptoms which include palpitations, light headedness, weakness, blurred vision, headache, extreme fatigue, nausea, syncope and sleep disturbance. The causal mechanisms are poorly understood and can overlap. POTS has been linked to autoimmune diseases and it is relatively common in young adult females.

Prior to 2014 one case following HPV vaccine had been published in a letter to the European Journal of Neurology. It described a patient developing symptoms two weeks following the first dose of HPV4.[46] In 2014 the same author (Blitshteyn) published a series of six cases, including the first case previously described. It is not clear how the patients were referred. The second case had onset 2 months after the third dose, the third case 5 days after the second dose, the fourth case four weeks after the first dose, the fifth case 5 days after the first dose and the sixth at 3 weeks after the first dose and worsening 3 months after the second dose.[47]

Brinth *et al* (2015) described 53 cases out of 75 patients referred to a syncope clinic. Patients were excluded if they could not account for a temporal association with vaccination and the onset of symptoms or had another possible triggering factor or had a chronic pre-existing illness. Patients who had an onset of more than 2 months since vaccination were also excluded.[48]

Later in 2015, Brinth *et al* published a collection of cases presenting for assessment for POTS after receiving the HPV vaccine and suspected HPV-induced illness. There were 35 women included, most of who had just completed heavy exercise. They did not check for

POTS prior to the study but symptoms were reported to have had onset of symptoms 0-30 days after vaccination with the time to examination ranging up to five-years. Statistical tests were used but how the patients were selected for analyses was not described. Twenty-one of the 35 patients fulfilled the diagnostic criteria for POTS.[49]

As these are case reports no conclusions about causality can be derived. The EMA review conclude there is an absence of evidence to suggest that HPV vaccine is a causal trigger for POTS and provide a detailed assessment of all the reports.[50]

The EMA reviewed the clinical trial data for HPV2, HPV4 and HPV9. There were over 60,000 subjects available for HPV4. The incidence of POTS in the HPV4 and HPV9 trials were less than 1 case per 10,000 person years and comparable to the placebo cohorts. Comparison of vaccinated and unvaccinated did not show an increased occurrence of POTS in the HPV group, nor a pattern of time-to-onset after exposure or patterns of clinical characteristics.[50]

Most of the POTS reports collected at the time of the EMA review came from a centre in Denmark and were published by Brinth.[48, 49] It was also noted that some of these cases better describe chronic fatigue syndrome,[50] which has been assessed as an AEFI following HPV2 vaccination using a self-controlled case series, and no association found.[51]

Since the EMA review, two important studies have been published which exclude an increased risk for POTS after exposure to HPV vaccine (below).

3.4.4.7 Experimental and observational studies that include POTS as possible outcome

In 2016, the safety of HPV9 from seven phase III studies included more than 15,000 subjects receiving more than one dose of vaccine were published (Moreira *et al*). Safety outcomes were followed for between 7 months and 72 months, depending on the study. New medical conditions were collected at each scheduled visit during the studies. Serious adverse events were collected over the duration of the studies. New medical conditions indicative of autoimmunity were collected. Two subjects who received the vaccine developed POTS, one case occurring over three years after vaccination.[25]

Cameron *et al* (2016) used the Scottish hospital admissions to assess the impact of HPV4 vaccination on the incidence of 60 diagnoses between 2004 and 2014. POTS was included as an outcome in this study. There were 246,954 girls who received three doses of the HPV vaccine between 2008 and 2014 and 12 admissions for POTS during the study period. These did not show an increase over expected levels in any of the years assessed.[52]

3.4.4.8 Case reports 2013-2016: Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is defined as a continuing pain that is disproportional to the inciting event and there may also be dysautonomic symptoms. The condition is usually restricted to a single limb. Most cases of CRPS follow a trauma event such as fractured limb immobilisation. It is often difficult to define and diagnosis is possible only after a time point when recovery from the initial injury should have occurred. An Australian case-series published in 2012 described five cases of CRPS, four of whom had been exposed to HPV4.[53] The time to onset was 0, 0, 0, and 4 days and symptom resolution occurred between 5 and 201 days. The authors concluded that intramuscular injection was sufficient in trigger the development of CRPS, rather than a

particular vaccine antigen. In other words the trigger was mechanical injury from injection. The immediate onset would support this conclusion.[53]

In 2014 Kinoshita et al published a case-series on 40 patients presenting with neurological complaints manifesting as headaches, fatigue, limb coldness and pain and weakness. Seven of these received HPV and 22 received HPV2. Three had biopsies, two of these showed pathology. Three had CRPS and POTS and one had POTS.[54]

A further two cases describing a fibromyalgia-like illness was published in 2014 by Martinez-Lavin et al,[55] who then went on to coin the term "HPV Vaccination Syndrome" in a report on a questionnaire-based study. The authors recruited cases from anti-immunisation websites and organisations who had complained of becoming ill with the symptoms of interest after vaccination; 45 individuals filled out questionnaires. The authors concluded they had evidence for a disabling syndrome after HPV vaccination.[56]

3.4.4.9 Experimental and observational studies that include CRPS as possible outcome

The Moreira report in 2016 on the safety of HPV9 from seven phase III studies that included over 15,000 individuals reviewed potential cases of CRPS. Two subjects were diagnosed with CRPS, both cases were attributed to a previous injury.[25]

3.4.5 Safety of nonavalent human papillomavirus vaccine

3.4.5.1 Safety in females

The nine-valent HPV vaccine was assessed in an international double-blind, phase IIb/III study of 14,215 women aged 16–26 years of age for immunogenicity, efficacy and safety (Joura 2015). Participants received either HPV9 or HPV4 at 0, 2 and 6 months. There were two serious adverse events and five deaths in each group. None of the deaths were considered vaccine related. The five deaths in the HPV9 group were as a result of suicide, acute lymphocytic leukaemia, traffic accident, hypovolemic shock and septic shock and sudden death. All occurred at between 15 days to 678 days after vaccination. In the HPV4 group the deaths were as a result of airplane accident, spinal cord injury, gastric adenocarcinoma, cervical spinal cord injury and cerebral haemorrhage. The deaths occurred between 7 days and 1114 days after vaccination.[57]

3.4.5.2 Safety in pregnancy

During the phase IIb/III study, there were a total of 1192 pregnancies in the HPV9 group and 1129 pregnancies in the HPV4 group. Information was available on 85% of these pregnancies. There were no differences in the proportions of participants with live births, delivery complications, spontaneous abortions or late fetal deaths. There were 20 congenital abnormalities reported in the HPV9 group and 21 in the HPV4 groups.[57]

3.4.5.3 Safety in males

A bridging study was conducted to evaluate the reactogenicity of HPV9 in males aged 16-26 years when compared with females of the same age. The study enrolled 1419 males and 1101 females. Serious adverse events were collected up to six months following the last vaccination. Injection site reactions were lower among men than women and most mild to moderate in intensity. Headache and pyrexia were the most common systemic events. There were no vaccine–related serious events and no deaths occurred thought the study.[58]

3.4.5.4 Concomitant use

A 2014 systematic review of HPV vaccines and coadministration found four studies of HPV4 which included the concomitant use with hepatitis B (HepB), tetanus-diphtheria-acellular pertussis-inactivated poliovirus (Tdap-IPV) and quadrivalent meningococcal conjugate (MCV4) vaccines. There were no significant increases in overall reactogenicity including both local injection site reactions and systemic events in coadministered groups. There were no studies for coadministration with influenza or measles-mumps-rubella (MMR) vaccines.[59]

HPV9 was assessed concomitantly in an open-label randomised multi-centre study with combined diphtheria, tetanus, pertussis and polio vaccine in 1054 adolescents 11 to 15 years of age. The Tdap-IPV vaccine was Repevax® (Sanofi Pasteur). Oral temperature was recorded for five days, injection site reactions and systemic events were rescored for a total of 15 days. Serious events were collected for the duration of the study. No deaths were reported. There were 16 serious adverse events, none were vaccine related. Concomitant vaccination resulted in higher numbers of injection site reactions (94% in the concomitant group vs. 90% in the nonconcomitant group). The intensity of the reactions was mild to moderate. There were no discontinuations due to adverse events.[60]

Concomitant administration of HPV9 with Tdap (Adacel®, Sanofi-Pasteur) and quadrivalent meningococcal conjugate vaccine (MCV4; Menactra®, Sanofi-Pasteur) in an open-label randomised multicentre comparative study. Participants received either HPV9 alone or HPV9 with MCV4 and Tdap in the opposite arm. Safety data was collected by diary care and visits at 1, 2 and 6 months. No deaths were reported. Five participants in the HPV9-only groups and five participants in the concomitant group reported serious adverse events. None were vaccine-related. There was a statistically significant difference in injection site swelling with 14% of HPV9 only participants and 9% of concomitant participants reporting swelling. Given this observation has been made previously (above) with coadministration of a Tdap-IPV vaccine, it is likely to be due the Tdap rather than MCV4 vaccine. Other events were comparable.[61]

3.5 Summary of safety

HPV vaccines have demonstrated excellent safety profiles. The pivotal clinical trials found no difference in rates of serious adverse events between vaccine and placebo groups. Extensive post-marketing studies to 2012 found no safety signals raised since the vaccines were licensed and a number of large investigations have assessed specific outcomes, particularly autoimmune conditions. Globally, post-marketing surveillance systems continue to monitor the safety of HPV vaccination programmes.

A summary of the published post-licensure safety data on HPV4 from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults. The review concluded syncope to be associated with the vaccine, and possibly skin infections, of which, more detailed analysis suggested some were likely injection site reactions. Serious events were carefully examined with no increase in incidence over background rates.

The pivotal clinical trials of HPV9 have found the vaccine more reactogenic than HPV4 with injection site reactions and common systemic events (headache, pyrexia, nausea, dizziness and fatigue all slightly higher in the HPV9 groups at rates between 2.3 and 5%,

with the exception of headache which occurred in 14.6% of participants. No serious adverse events were found associated with HPV9.

Clinical trial and post-licensure data show both HPV4 and HPV9 to be safe in pregnancy. Reports show that the rates of spontaneous abortions, birth defects and other outcomes are comparable to those in the general population. Pregnancy outcomes were similar among HPV9 and HPV4 recipients, similar to the placebo groups from the HPV4 trials and within expected ranges reported for pregnant women.

The possible association between HPV vaccine and venous thromboembolism has been extensively investigated using robust methods and large populations; the data do not support a causal association.

This review considered perceived issues around the safety of HPV vaccines that have arisen since 2012. Because infectious agents and molecular mimicry are known triggers for the onset of autoimmune conditions a role for vaccines is biologically plausible. While the large scientific post-marketing safety studies have not found any increased risk for autoimmune conditions following exposure to HPV vaccine, concerns about the development of autoimmune diseases after HPV vaccination, based on sporadic case reports, have been fuelled by social and news media.

The possible association between HPV vaccine and MS has been investigated using robust epidemiological methods with large populations, and although one study found an increased risk in a thirty day period following vaccination, overall the data do not support a causal association. Similarly, there is no evidence that HPV vaccine increases the risk for SLE.

Two cases of acute disseminated encephalomyelitis (ADEM) occurring at widely different temporal intervals after HPV vaccination were published, do not provide evidence for a causal association. The large post-marketing surveillance studies have not detected ADEM as an outcome.

A series of cases of primary ovarian failure with variable temporal onsets months to years later have been published. Empirical studies have not found a safety signal.

Prior to 2014 one case of POTS following HPV vaccine had been published in a letter to the European Journal of Neurology. It described a patient developing symptoms two weeks following the first dose of HPV4. Since then many cases have been published, largely by the same authors. A major review by the EMA that included over 60,000 subjects available for HPV4 found that the incidence of POTS in the HPV4 and HPV9 trials were less than 1 case per 10,000 person years and comparable to the placebo cohorts.

Since the EMA review, two important studies have been published which exclude an increased risk for POTS after exposure to HPV vaccine, one clinical trial data on over 15,000 vaccinees and the other a cohort study of almost quarter of a million girls who had received three doses of vaccine. There was no signal for POTS found in either of these studies.

In addition to POTS, a series of cases of CRPS with variable temporal onsets have also been published. As with the other case reports, empirical studies have not found a safety signal. Among 15,000 clinical trial participants who received HPV vaccine, two subjects were diagnoses with CRPS and both cases were attributed to a previous injury.

The observational studies to date have concluded there is no association between HPV4 vaccination and the development of autoimmune conditions. It must be noted that some

of the conditions are rare and the development of initial symptoms can be non-specific making determination of onset and diagnosis difficult. However, the consistently low numbers of reported cases in comparison to the expected background rate and the large numbers of exposures to HPV4 suggest a lack of association.

Previous studies found coadministration of HPV4 with other vaccines to be safe. Concomitant use of HPV9 has been assessed with Tdap-IPV, Tdap, MMR, HepB and MCV4 vaccines with no safety concerns.

Extensive international data to date continue to support the excellent safety profile of HPV vaccines.

4 Immunogenicity

4.1 Objective

The objective of this section is to review the most recent immunogenicity data for HPV4 and HPV9. The focus will be on the non-inferiority of nonavalent versus quadrivalent vaccines, different schedules, and performance in the immunocompromised.

4.2 Outcomes

The outcomes considered for this review are:

- Geometric mean titres
- Seroconversion

4.3 Review

4.3.1 Non-inferiority of two and three-dose schedules

A systematic review and meta-analysis published in 2015 compared two and three-dose HPV vaccine immunisation schedules in preadolescent females and reported that the evidence of non-inferiority was inconclusive at all subsequent time points (36 and 48 months follow-up). The review found that geometric mean titres (GMTs) of vaccine-type HPV antibodies were higher after three doses of vaccine than two doses at the same time point in the same age group. Also, GMTs were higher after three doses in girls vaccinated at 9-14 years of age than three-doses in young women aged 15-26 years. A fast decline in GMT was seen for all dosing schedules and age groups during the first year, which continued for at least 4 years after the first dose. Non-inferiority was supported when a two-dose schedule given to girls was compared with three doses given to young women. However, non-inferiority was not established when comparing two and three-dose schedules in the same age group. For two-doses of HPV4 vaccine, HPV-18 antibody levels were not non-inferior to three-doses from 18 months onwards. The authors concluded that two-dose HPV vaccination would need close monitoring to ensure clinical effectiveness.[62]

Specifically, with respect to the HPV-18 antibodies, a study reporting the durability of non-inferiority found that antibody responses in girls after two doses were non-inferior to three doses for all four vaccine genotypes at 7 months, but not for HPV-18 by 24 months or HPV-6 by 36 months after the last dose.[63]

A multicentre prospective cohort study in India (2016) investigated the immunogenicity and efficacy of one, two and three doses of HPV4 (Gardasil®) in 17,729 girls aged 10-18 years of age. The immune response to two doses was non-inferior to three doses at 7 months post vaccination, but was inferior at 18 months. Short-term protection provided by one dose against persistent HPV infection was similar to that afforded by two or three doses. The incidence of HPV infections in 2649 cervical samples was similar irrespective of the number of vaccine doses received, and was around 10 times lower than for non-vaccine HPV types. The study concluded that the findings supported the WHO recommendations of at least two doses at least 6 months apart.[64]

4.3.2 Alternative three-dose schedules

The rationale for the optimal immunisation schedule is based on the time for affinity maturation and development of immunological memory. The first one (or two) doses are to prime and initiate the development of affinity maturation and the subsequent dose is placed at least 4 to 6 months later in order to stimulate a secondary response of high affinity immunological memory. Experience with hepatitis B vaccines supports the long term effectiveness of a two dose series given at varying intervals. The duration of antibody does not correlate with protection which is observed even when antibody has waned to undetectable levels.[65]

A non-inferiority trial investigated alternative three-dose schedules of HPV4 vaccine in 518 Vietnamese adolescent girls aged 11-13 years (given at 0-3-6 months, 0-6-12 months or 0-12-24 months, compared with standard 0-2-6 months regime). Similar antibody concentrations were found after 29 months or longer for all dosing schedules. For the 0-12-24 schedule, pre dose three antibody levels were similar to those measured at 32 months after dose three. It was concluded that extended schedules did not result in inferior immune responses. The authors also suggested that two doses of HPV4 might afford similar protection when delivered at 0 and 12 months.[66]

A follow-up study conducted in Colombia evaluated the long-term immunogenicity and effectiveness of three doses of HPV4 vaccine in women immunised at age 24-45 years (n=684) or 25-50 years (n=651). Findings showed that HPV4 was effective against genital warts and cervical dysplasia for at least 6 years and immunogenicity persisted against vaccine-targeted HPV types. At a 72-month follow-up, the proportion of vaccinated participants aged 35-45 years with IgG antibodies against HPV-6, HPV-11, HPV-16 and HPV-18 (88.9%, 90.4%, 97.1% and 42.7%, respectively) was similar to those aged 24-34 years (89.4%, 94.4%, 97.5%, 48.5%, respectively), as detected by competitive Luminex® immunoassay (cLIA).[67]

Current evidence supports flexibility in the dosing schedules for HPV4 to 12 months post dose one.[65]

4.3.3 Immunogenicity in adult men

Following a study in men investigating the natural history of HPV infection, 145 men aged 27-45 years (median age 36 years) were vaccinated with three doses of HPV4 vaccine (Gardasil, 0-2-6 month schedule) in the US and Mexico. As determined by cLIA, levels of anti-HPV-6, -11, -16 and -18 antibodies were comparable to those observed in younger men and did not differ by age group or sexual orientation at 7 months post vaccination. Seroconversion occurred in all participants to the four vaccine-target HPV types. At the time of vaccination, 16.6%, 4.8%, 13.1% and 6.9% of participants had pre-existing antibodies against HPV-6, -11, -16, and -18, respectively; these men had

higher titres following vaccination than those who were seronegative prior to vaccination.[68]

Antibody response to HPV4 in men does not differ by age or sexual orientation and is comparable in older men to the response in men under 27 years of age.

4.3.4 Immunogenicity in the immunocompromised

4.3.4.1 HIV infection

Immunogenicity of HPV4 vaccine was compared in HIV-infected and HIV-negative adolescents and young adults aged 14-27 years in Italy. Three doses were administered at 0, 2 and 6 months. No significant difference was determined between groups; one month after third dose of vaccine, seroconversion rate was 0.85 in the HIV-infected group (n=46) and 0.91 in the HIV-negative group (age and gender matched controls, n=46; p=0.52). Consistent with this, no significant differences between groups in anti-HPV IgG titres were seen at 12 and 18 months after dose one.[69]

An open-label phase II study assessed the immunogenicity of HPV4 vaccine in 99 women aged 16-23 years with HIV-infection and was compared with an historical group of 267 HIV-negative controls. The participants were HPV seronegative and DNA negative for each HPV type. GMTs were lower in participants not receiving antiretroviral therapy (ART) for HPV-16 and -18; no differences were noted for those taking ART. Seroconversion rates were 100% for those taking ART for HPV-6, -11, -16 and -18. For those not on ART, seroconversion rates were 92.3%. 94.4%, 97.1% and 100% for HPV-18, -16, -11 and -6, respectively. Seroconversion rates and GMTs for those not on ART were significantly lower for HPV-18 than the historical controls.[70]

A US-based study found, among HIV-infected women with CD4 counts >200 cells/µl (age 13-45 years, median age 36 years), that women with lower HIV-RNA loads (<400 copies/ml) had better seroconversion proportions for HPV-11, -16 and -18 than those with high viral loads (>400). Among women with low CD4 counts (<200 cells/µl), significantly lower antibody titres were noted against HPV-6. Low seroconversion rates were observed in women with HIV RNA load of >10,000 copies/ml and/or CD4 counts <200 cells/µl and a tendency for lower HPV antibody titres. However, there is no defined correlate of protection to predict how seroconversion or antibody titres relate to clinical protection.[71]

Seroconversion among HIV infected individuals has been demonstrated to be robust and higher among those with lower HIV viral loads or on ART.

4.3.4.2 Immunocompromised children

Immunogenicity and persistence of immunity against HPV4 vaccine was assessed in children aged 5-18 years (mean age 12.3 years) with a range of immunocompromising conditions who were given three doses of HPV4. Of the 59 cases enrolled, transplant recipients included 13 liver, 16 kidney, 20 haematopoietic stem cell transplant (HSCT) recipients, seven had juvenile idiopathic arthritis (JIA) and three had inflammatory bowel disease (IBD). Prospective liver transplant patients were given a first dose prior to transplant, whereas the other transplant recipients including HSCT were given dose 1 at least 6 months after transplant. Subsequent doses in all patients were given at 2 and 6 months after dose 1. One patient with chronic kidney disease at the time of enrolment underwent kidney transplant after completion of HPV immunisation. Thirteen participants were on one immunosuppressive agent (22%), 24 participants were on one or more

(40.7%) and the remainder (n=21) were not being treated with immunosuppressive drugs or the data was missing. Only one patient was not HPV seronegative at baseline. One month after dose three (7 months after first dose), all patients had elevated GMTs with the greatest increase in titre for HPV-16 (from 11.6 mMU at baseline to 3066 mMU at 7 months) and the lowest for types 6 and 18 (from 11.4 to 473 and 10.1 to 473 mMU, respectively). GMTs declined over the following months but remained at least four-fold higher than baseline at 24 months post dose one. All antibody titres were significantly lower in female compared with males at 7 months and for types 16 and 18 at 24 months. All antibody titres were lower at 7 and 24 months for patients being treated with immunosuppressive drugs. No significant differences in antibody titres were seen between the <12 years and ≥12 years age groups. When compared with healthy children of the same age groups, antibody titres were lower in the immunocompromised children and particularly females.[72]

The immune response to HPV4 among immunocompromised children appears adequate.

4.3.4.3 Organ transplant recipients

In a small study in the US, HPV4 was shown to be immunogenic in solid organ transplant recipients aged 9-17 years on stable immunosuppression at least 6 month post-transplant. A total of seven kidney and two liver recipients completed the full vaccine course of three doses. Transplant recipients demonstrated 100% seroconversion and similar GMTs for vaccine-type HPV antibodies after receiving two or three doses of vaccine compared to historical healthy controls.[73]

A Canadian study investigating vaccination with HPV4 in adult transplant recipients found immunogenicity to be relatively low. Vaccine response (seropositivity rates) were 63.2%, 68.4%, 63.2% and 52.6% at four weeks after the third dose of vaccine against HPV-6, 11, -16, and -18, respectively. Solid organ transplant patients aged 18-35 years, at least 3 months post-transplant and on stable immunosuppression, were immunised at enrolment, 2 and 6 months. Responses to all four HPV types were seen in 18/38 (47.7%) of patients. Vaccine response tended to be lower in lung (15/18, 83.3%) than kidney transplant recipients (4/7, 57.1%), and these patients responded to fewer vaccine types than the other transplant types (median 1 versus 4, p = 0.038). However, the numbers of lung transplant recipients in this study were low. The rates of seropositivity were significantly lower than reported in other RCTs for healthy individuals (>90%), particularly for early transplant and lung transplant. Another factor associated with low responses was higher tacrolimus levels.[74]

Older organ transplant recipients produce suboptimal responses to HPV4. Recommendations may include consideration of pre-transplant vaccination or vaccination at a younger age.

4.3.4.4 Autoimmune disease

A systematic review assessed the immunogenicity of HPV vaccines in patients with a range of autoimmune diseases, including systemic lupus erythematosus (three studies), JIA (two studies), and IBD (one study). Of these studies, three investigated HPV4 and two investigated HPV2 vaccines. One study did not find significant differences with case-controls in seroconversion rates for 50 SLE patients, although, patients receiving immunosuppressive therapeutics had lower anti-HPV antibody titres following vaccination. This discrepancy was most pronounced for patients treated with mycophenolate mofetil combined with low-dose prednisolone. In another study,

seroconversion rates in 16 SLE patients for HPV-6, -11, -16 and -18 were 94.4%, 100%, 100% and 94.4%, respectively, 1 month after dose three, and were comparable with healthy controls. It was noted that the patients in the first study were older than in the second (18-35 years versus 12-26 years) and there were differences in the concomitant therapies.[75-77]

The study investigating IBD was an open label study that enrolled 37 immunosuppressed patients aged 9-26 years on a range of immunosuppressive therapies. After three doses of HPV4 vaccine, all patients were seropositive for HPV-6, -11 and -16; two patients did not seroconvert for HPV-18. GMTs did not differ from healthy females. Serum samples taken up to 27 months after completion of the three-dose course from a second cohort of patients showed that all these IBD patients had remained seropositive in line with healthy vaccinees.[78]

While some immunosuppressive regimes can attenuate the immune response to HPV4 patients with autoimmune diseases generally appear to respond well to the vaccine.

4.3.4.5 Adolescents with chronic kidney disease

A cohort study examined immunogenicity of HPV4 in adolescent girls aged 9-21 years with chronic kidney disease (23 with chronic kidney disease, 9 on dialysis and 23 post kidney transplant) from 2008 to 2012. In the chronic kidney disease and dialysis group, antibody responses were generated for all four HPV serotypes up to 12 months and after 12 months after vaccination. Significantly fewer patients with transplants achieved seropositivity for HPV-6, -11 and -18 (63.6%, p=0.003; 63.6% p=0.003 and 72.7%, p=0.02, respectively) within 12 months of immunisation and at more than 12 months after dose 3 for HPV-6, -11, -16 and -18 (62.5%, p=0.02; 50%, p=0.001; 75%, p=0.04; 50%, p=0.001, respectively).[79]

Patients with chronic kidney disease and on dialysis were able to generate antibody responses to HPV4. Seropositivity was less well achieved post-transplant, there for it is recommended to vaccinate prior to renal transplantation.

4.3.5 Coadministration and immunogenicity

The immunogenicity of HPV4 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 has been previously evaluated and found to be well tolerated with no interference with the immune response to either vaccine.[80, 81] There are no concerns about co-administration of HPV4 with any other vaccines.

More recently, a 2014 systematic review found non-inferior immunogenicity when HPV vaccines were coadministered with additional vaccines including 4-valent meningococcal conjugate, hepatitis A and B. One double-blind and eight open-labelled RCTs published between 2008 and 2012 were reviewed, which included 144 - 1871 participants aged 9 to 25 years. Seroconversion rates of greater than 99.5% were reported for all studies with a control group that received HPV vaccine alone and non-inferior GMTs in the HPV vaccine coadministered groups for all vaccine HPV types. The immune response to non-HPV vaccines was also non-inferior.[59]

The immunogenicity of HPV4 vaccine in girls aged 9-10 years, when given concurrently or a month before combined hepatitis A and B vaccination (Twinrix®-Junior), was assessed in an open-labelled RCT in Canada (2014). The study found that when given

concurrently, a two-dose schedule (at 0, 6 months) induced a strong immune response to all the components of both vaccines in preadolescent girls. No significant difference was seen in anti-HPV seropositivity or GMTs between the two groups. Prior to the second dose, 6 months after a single dose of HPV4 vaccine, anti-HPV antibodies were detected in 94-100% of 207 participants (detectable antibody rates: 94%, 100%, 99% and 96% for anti-HPV-6, -11, -16 and -18, respectively). An anamnestic response was seen after the second dose of HPV vaccine in those who did not have detectable antibodies after the first dose – only four participants had undetectable anti-HPV-18 antibodies at 36 months post dose two. Overall, the second dose of HPV4 was of a high magnitude (55-100 fold increase in GMTs) and indicated good priming by the first dose.[82]

All data to date support the coadministration of HPV4 with other vaccines.

4.3.6 Immunogenicity of HPV9

The immunogenicity of investigational HPV9 was initially assessed in an international randomised double-blind phase IIb/III study in women aged 16 – 26 years (published by Joura, 2015). A total of 14,215 women were randomised to receive HPV9 or HPV4. Antibody responses generated by the HPV9 vaccine to HPV-6, -11, -16 and -18 were non-inferior to those generated by the HPV4 vaccine.[57]

To compare the immunogenicity of HPV9 with HPV4, a multicentre RCT double-blind phase III study measured the immunogenicity of HPV9 compared with HPV4 in 600 sexually naïve 9-15 year old females (mean age for dose 1 was 12.6 years). The girls were randomised to receive HPV9 or HPV4 vaccines. GMTs post dose 3 induced by each vaccine were similar for HPV-16 and -18 antibodies and were found to be non-inferior (anti-HPV-16 IgG: 6739.5 vs 6887.4 mMU/ml; anti-HPV-18 IgG: 195.6 vs 1795.6 mMU/ml, for HPV9 vs HPV4 vaccines, respectively; $p<0.001$). Anti-HPV-6 and -11 GMTs were also numerically similar and non-inferior between vaccines. Anti-HPV-16 and -18 GMTs were numerically higher in younger girls when stratified by age (9-12 and 13-15 years). All participants seroconverted for HPV6/11/16/18 after three doses of either vaccine. All participants, who received HPV9 vaccine seroconverted to the additional vaccine HPV types (31/33/45/52/58), except one who did not seroconvert to HPV-45 and had lower immune responses to the other HPV types. Although GMTs were low, those who received HPV4 vaccine responded at some level to the HPV types not included in this vaccine; seroconversion rate for HPV-31 and 58 were 73.5% and 54.8%, respectively, indicating moderate cross-protection.[83]

The immunogenicity of HPV9 vaccine and non-inferiority between males and females was assessed in a multicentre study conducted in 17 countries during 2009 to 2013 (published 2015). The study enrolled three cohorts: sexually naïve girls and boys aged 9-15 years and young women aged 16-26 years (the age used in pivotal clinical trials to establish vaccine efficacy); each received three doses of HPV9 on a 0-2-6m schedule and immunogenicity was assessed at month 7. A total of 1875 girls, 647 boys and 444 young women were fully vaccinated. Findings showed that GMT responses for all nine vaccine HPV types in girls and boys were non-inferior to young women. By month 7, more than 99% of participants had seroconverted against all nine HPV types, and although GMTs declined by 10-20% between month 7 and month 36, more than 90% of participants were seropositive at month 36 for the nine HPV types.[84]

HPV9 vaccine was assessed for immunogenicity in 1106 young heterosexual men (HM) and compared with 1101 young women at the same age of 16-26 years. The international study also evaluated the immunogenicity in 313 men who have sex with

men. All participants received three doses of HPV9 at 0, 2 and 6 months. Findings showed that at month 7, GMTs and seroconversion rates against all nine HPV types in HM were non-inferior to those of the women ($p<0.001$ for each). For MSM, although GMTs were numerically lower at month 7, over 99.5% were seropositive for each HPV type.[58]

HPV9 has demonstrated non-inferiority to HPV4 in males and females. MSM appear to produce lower GMTs than HM, possibly due to greater exposure to the virus and the phenomenon of original antigenic sin, highlighting the importance of vaccination at a young age.

4.4 Summary of immunogenicity

Although there is no known correlate of protection, HPV vaccines generate good antibody responses in most recipients, even those who are moderately immunosuppressed. Two doses are more immunogenic in recipients aged between 9-15 years than older age groups and comparable to three doses in older recipients. A decline in antibody levels is observed within one year of immunisation. In young females, two doses have been found to be non-inferior to three doses, particularly when the interval between doses is more than 4 months. There are some differences between the HPV types and HPV-18 appears to be less immunogenic in some situations, particularly for older women, than the other vaccine-types. Generally, younger recipients have a better response than older adolescents and adults.

Current evidence supports flexibility in the dosing schedules for HPV4 to twelve months post dose one and all data to date support the coadministration of HPV4 with other vaccines.

Antibody response to HPV4 in men does not differ by age of sexual orientation and is comparable to the response in men under 27 years of age.

Difference in seroconversion rates and antibody titres were seen in immunocompromised individuals. In some cases, differences were seen in antibody response to certain HPV-types. The immune response to HPV4 among immunocompromised children appears adequate. Seroconversion among HIV infected individuals has been demonstrated to be robust and higher among those with lower HIV loads or on ART. While some immunosuppression regimes can attenuate the immune response to HPV4 patients with autoimmune diseases generally appear to respond well to the vaccine. In contrast, older organ transplant recipients produce suboptimal responses to HPV4. Recommendations may include consideration of pre-transplant vaccination or vaccination at a younger age. While some immunosuppression regimes can attenuate the immune response to HPV4 patients with autoimmune diseases generally appear to respond well to the vaccine.

The immunogenicity of investigational HPV9 was initially assessed in a randomised, international, double-blind, phase IIb/III study in women 16 – 26 years of age. Antibody responses generated by the HPV9 vaccine to HPV-6, -11, -16 and -18 were non-inferior to those generated by the HPV4 vaccine. HPV9 has demonstrated non-inferiority to HPV4 in males and females. Men who have sex with men appear to produce lower GMTs than heterosexual men, possibly due to greater exposure to the virus and the phenomenon of original antigenic sin, highlighting the importance of vaccination at a young age.

5 Efficacy

5.1 Background

Vaccine efficacy is the percent reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal conditions, usually a randomised controlled trial (RCT). It is distinct from vaccine effectiveness which is measured under real-world conditions.

5.1.1 Efficacy findings prior to 2013

5.1.1.1 Efficacy in young women

Prophylactic efficacy of HPV4 was evaluated in the pivotal Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II studies which enrolled participants during 2002 to 2003.

FUTURE I included 5455 women aged 16 to 24 years with the primary endpoints of: incidence of genital warts; vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial neoplasia; adenocarcinoma *in situ*; or cancer associated with HPV types 6, 11, 16 or 18.[85] FUTURE II included 12,167 women randomised to HPV or placebo with a primary endpoints of CIN2 or 3, AIS or cervical cancer related to HPV-16 or -18.[86]

Four year efficacy was assessed in 17,622 women from the FUTURE studies. 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).[87]

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).[87]

The effect of HPV4 on the risk of subsequent disease following diagnosis or procedure for disease was evaluated in 2,054 women among 17,622 participants in the FUTURE I and II studies who 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 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.[88]

5.1.1.2 Efficacy in women aged 24 – 45 years

All sexually active women are at risk for HPV acquisition despite the peak incidence occurring within 5 – 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 to 41.9), respectively, as infection and disease were present at baseline. HPV4 has high efficacy in older women who are not infected at baseline.[89]

5.1.1.3 Efficacy 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. 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).[90]

Men who have sex with men are at higher risk for HPV infection, anal cancer and high-grade AIN. 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 to 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.[91]

A small prospective RCT investigated the efficacy of HPV vaccine in preventing reinfection with genital warts. The study enrolled 171 men in Turkey with genital warts (mean age 34 ± 7.6 years, 111 single and 60 married), and after initial treatment, 91 randomly selected to receive three doses of HPV4 vaccine; 80 were unvaccinated. The study found that vaccination status did not significantly influence wart recurrence, whereas married men had significantly more recurrences. This was the only explanatory variable that was associated with recurrence.[92]

In pivotal efficacy trials HPV4 demonstrated high efficacy against all endpoints in both males and females, as well as effectiveness in reducing the risk for subsequent HPV related disease.[90]

5.2 Objectives

The objectives of this section are to summarise the most recent studies evaluating efficacy of HPV4 among different population groups, including older age groups and present efficacy for HPV9 published since 2013.

5.3 Outcomes

Outcomes considered are:

- HPV Infection
- Genital warts
- Cervical cytological abnormalities
- Cervical histological abnormalities
- Cancers

No recent literature on efficacy appears to have been published specifically related to male cancers or genital warts in males.

5.4 Review

Several reviews of HPV4 efficacy studies have been published since pivotal licensure trials.

5.4.1 Efficacy in previously infected women

Efficacy against anogenital pre-cancer (CIN3+) in women with evidence of prior vaccine-type HPV exposure was explored in a systematic review (2014). Women with prior exposure to vaccine-type HPV over a 3-4 year period in three RCTs and two post-trial cohort studies, consisting of 13,482 women who had evidence of HPV infection at the entry to these studies. There was no evidence that HPV vaccines were effective in preventing vaccine-type HPV associated pre-cancer in pre-exposed women. Despite these findings, longer-term benefit in preventing re-infection could not be excluded.[93]

5.4.2 Efficacy of HPV9 in women

Since the recommendations and widespread introduction of HPV4 placebo-controlled trials are no longer an ethical approach for studying HPV vaccines. The efficacy of HPV9 had to be assessed alongside the HPV4 comparator. Efficacy was assessed in 14,215 women aged 16 to 26 years in a double-blind, phase IIb/III trial. Three doses of either HPV4 or HPV9 occurred at 0, 2 and 6 months. In the per-protocol efficacy population, the incidence rate of high-grade disease related to HPV-31, -33, -45, -52, and -58 was 0.1 per 1000 person-years in the HPV9 group and 1.6 per 1000 person-years in the HPV4 group (1 case vs 30 cases). HPV9 efficacy was 96.7% (95% CI 80.9 to 99.8).[57]

5.5 Summary of efficacy

HPV vaccines do not appear to prevent the development of precancer in women already pre-exposed to HPV. However, there may be some benefit if preventing reinfection or infection with different HPV types.

In comparator studies, HPV9 efficacy was shown to be 96.7% (95% CI 80.9 – 99.8%) against high-grade disease caused by the additional HPV types in this vaccine compared with HPV4, which does not contain the additional types (HPV-31, -33, -45, -52, and -58).

6 Effectiveness and impact

6.1 Background

The effectiveness of a vaccine is assessed using observational study methods where vaccinated individuals are compared with unvaccinated individuals in a real-life setting. Effectiveness of a vaccine is different from the impact of a vaccine, which evaluates the impact on the populations and is really a reflection of the immunisation programme as a whole. Impact depends on a range of factors, in particular, coverage, population dynamics and herd immunity. Impact uses cross-sectional ecological data.

Given the variables that affect the impact of a vaccine programme, the reported impact from different countries varies. What is consistent is the clear positive association between vaccine coverage and impact.

Vaccine effectiveness, and impact, are measured after the implementation of a vaccination programme and, depending on the endpoints being measured, become evident over time. In 2012 there had been around four years' practice of HPV vaccine use. As of 2016, there is a further three and a half years of international experience.

6.2 Objectives

The objectives of this section are to assess global experiences with HPV immunisation in terms of effectiveness in preventing disease and the impact of coverage on herd immunity and prevalence of vaccine-type HPV infection.

6.3 Outcomes

Outcomes considered are:

- HPV Infection
- Genital warts
- Cervical cytological abnormalities
- Cervical histological abnormalities
- Cancers

Data on effectiveness against other cancers are not yet available.

6.4 Review

A 2016 systematic review of literature summarised the global experiences with HPV4 from the literature published from 1 January 2007 to 29 February 2016. It assessed the global effect of HPV4 vaccine on HPV infection, genital warts and cervical abnormalities based on 57 publications across nine countries. The greatest impact was seen in countries with high vaccine uptake and among girls vaccinated prior to HPV exposure. Maximal reductions of around 90% were reported for vaccine-type HPV infections (HPV-6/11/16/18) and genital wart cases.[94]

6.4.1 HPV infection

Australia has published two studies on HPV infections since 2013.[95, 96] Within 6 years of HPV4 vaccine availability in Australia, a decrease of 86% was observed in prevalent HPV6/11/16/18 infections among women aged 18-24 years after three doses of vaccine and a decrease of 76% was observed following at least one dose compared with unvaccinated contemporaries. In Australian-born women aged under 21 years, HPV-6 and -11 disappeared and remained at 0% and HPV-16 and -18 was detected in ≤5% of samples collected during 2008 and 2009. The three-dose strategy was considered sufficient for the HPV4 types to almost disappear in the younger cohort within 3 years of introduction of the vaccine programme. A significant herd effect was also noted.[96]

In a German population-based cross-sectional study, 787 participants were recruited by invitation and tested via home collection for 18 high-risk (hr) and six low-risk (lr) HPV strains. Both HPV2 and HPV4 have been used routinely since 2007. In non-vaccinated women aged 20-25 years, HPV prevalence of any type was almost 40% and prevalence of hr-types was 34%. Among participants aged 20-21 years, HPV-16/18 prevalence was significantly lower in women who reported to be vaccinated than in non-vaccinated women. After adjustment for risk factors HPV vaccination was significantly associated with a lower risk for HPV-16/18 infection in the youngest age group, supporting the vaccination of girls in early adolescence.[97]

Sweden introduced HPV vaccination in 2010; prior to that HPV vaccination was available on-demand from 2006. HPV type prevalence was followed from 2008 to 2013 using a national register for *Chlamydia trachomatis* screening. Most women on the registry are aged 13 to 22 years. Samples were screened for two lr HPV types and 14 hr types. There were 44,146 samples in 2008, 5,224 in 2012 and 5815 in 2013. HPV-6 prevalence in these samples decreased from 7.0% in 2008 to 4.2% in 2013 (-40.0%; $p<0.0005$). HPV-16 decreased from 14.9% to 8.7% (-41.6%; $p<0.0005$) and HPV-18 decreased from 7.9% to 4.3% (-45.6%; $p<0.0005$) among women aged 13 to 22 years. Two non-vaccine HPV types (HPV-52 and HPV-56) were increased among women aged 13 to 22 years, both in 2012 and 2013. There was a significant reduction in HPV-6, -16, and -18 prevalence associated with a concomitant increase in HPV vaccination coverage. The authors noted the minor changes seen for non-vaccine types would require further investigation.[98]

The US has published eight studies on HPV infection, five since 2013.[99-101] Similar to Sweden, reductions were observed in the US following at least one dose (89% in females aged 14-24 years). Decreases in vaccine-type HPV infections of 17-49% were also observed in unvaccinated women potentially reflecting herd protection.[94]

Additionally, a 2015 systematic review and meta-analysis investigated the population level impact and herd immunity effects of HPV vaccination programmes based on 20

eligible studies as reported in published literature from January 2007 to February 2014. In countries with female vaccination coverage of at least 50%, the review found that HPV-16 and -18 infections decreased significantly by 68% (relative risk RR 0.32; 95% CI 0.19-0.52) and genital warts decreased by 61% (RR 0.39; 0.22-0.71) in girls aged 13-19 years. Cross-protection was suggested, with significant reductions in non-vaccine HPV types-31, -33 and -45. Herd effects were observed with significant reductions in genital warts in unvaccinated boys (aged <20 years) and women aged 20-39 years. Although significant reductions were reported in HPV-16 and -18 infections and in genital warts in girls aged <20 years, there was no indication of cross-protection or herd effects in countries where HPV vaccine coverage was less than 50%.[3]

Successful implementation of HPV vaccination programmes are associated with significant reductions in the prevalence of vaccine-type HPV, particularly among the cohorts eligible for vaccination and where coverage is highest.

6.4.2 Genital warts

Australia has published eleven studies on the impact of HPV vaccination on genital warts, eight since 2013.[102-106] Of note, the impact of HPV vaccination has been similar in Indigenous females,[106] and the relative reduction across different levels of disadvantage are similar.[107]

As would be expected, decreases in HPV-6/11 infection rates are closely matched by declines in the incidence and prevalence of genital warts. In Australia and Denmark, with high vaccine uptake, yearly decreases of around 50% were reported in several studies of women aged <21 years. Four years after vaccination programme implementation in Australia, up to 92.6% reduction in genital warts cases was observed. In countries with moderate to low uptake, the reductions in genital warts were lower, and dependent on setting, age group and time-period considered. Reductions were mainly observed in vaccinated women, although some studies found evidence of herd immunity. Generally, the highest effectiveness against genital warts was observed following three-doses of HPV4 vaccine (76%-93%).[94]

An earlier systematic review in 2014 examined the evidence of direct and indirect impact of HPV4 vaccine on genital warts based on published literature between January 2009 and August 2014 across six countries. Data from the clinical trials demonstrated a rapid reduction in genital wart incidence, particularly in the target populations. In Sweden, vaccine effectiveness against genital warts was highest in girls vaccinated before the age of 14 years (93%). Herd protection was also suggested for unvaccinated male and older females, however, it was not observed in all countries. For example, in Denmark factors other than vaccination may have had contributed to herd protection. In Australia there have been no cases of genital warts diagnosed in women under 21 years reported as being vaccinated.[108, 109]

An analysis of genital wart management rates in Australian general practices showed a 61% decrease, from 4.33 cases per 1000 encounters pre-programme (July 2002 - June 2006) to 1.67 per 1000 post-programme (July 2008 – June 2012), since the introduction of the HPV4 vaccination programme for women aged 15-27 years. For vaccine-eligible women, there was a significant year-on-year reduction in the rates of genital warts management ($p<0.0001$). For all other age-sex groups, there was no significant change in management rate of genital warts between the pre-programme and post-programme periods.[105]

High HPV4 vaccination coverage has been associated with dramatic reductions in the diagnosis of genital warts. Data from Australia suggest elimination is possible.

6.4.3 Cervical intraepithelial neoplasia and cancer

The 2016 systematic review mentioned above also assessed the global effect of HPV4 vaccine on HPV infection and cervical abnormalities. For cervical abnormalities, maximal reductions of 85% were reported for histologically-proven high-grade cytological abnormalities and of approximately 45% for low-grade cytological abnormalities. In comparison with unvaccinated females, overall declines of 34% of low-grade and 47% of high-grade cervical cytological abnormalities were shown in cohorts of females vaccinated at ages 12-26 years within the first 5 years of the HPV4 vaccination programme. The largest declines were observed in females aged 20-23 years. Reductions as high as 57% and 80% for CIN2+ and CIN3+ lesions, respectively, were reported in the youngest cohorts vaccinated shortly after programme implementation in Australia and Denmark, countries with high and timely vaccine coverage.[94]

A cohort study in Denmark found that the risk of cervical atypia or CIN2/3 was significantly reduced among HPV4 vaccinated women born from 1981-1994. The 1989-1990 birth cohort also had a statistically significant reduced risk of atypia or worse, and the risk of CIN2/3 was decreased but not significantly. No cervical neoplasia were seen in the 1997-1999 cohort, and the number screened were very small. Overall, in the Danish population born during 1989-1999, women who received at least one dose of HPV4 vaccine showed statistically significant reductions of up to 60% in risk for atypia and up to 80% in risk for CIN2/3 compared with unvaccinated women. HPV4 vaccination was licensed in 2006 in Denmark and funded for girls aged 12 years from 1 January 2009 (1996-1997 birth cohort), a catch-up campaign was begun in 2008 for girls aged 13-15 years (1993-1995 cohorts). The findings indicated an early effect of HPV vaccination.[110, 111]

Population-based surveillance in the US found a significant reduction in the prevalence of HPV-16/18 CIN2+ lesions among women who had received at least one dose of HPV vaccine, but this was not observed among unvaccinated women. The population-based data support an increasing vaccine effectiveness with increasing dose between first vaccination and the detection of cervical disease.[112]

A Canadian study provides strong evidence for the early benefits of HPV vaccination against cervical dysplasia among girls aged 14 -17. Administrative health databases in Ontario included a population-based retrospective cohort of 131,781 girls ineligible and 128,712 girls eligible for the HPV vaccination programme. There were 2436 cases of dysplasia. Vaccination significantly reduced the incidence, a relative reduction of 44% (RR 0.56; 036-0.87). The program eligibility also had a significant protective effect.[113]

The impact of HPV immunisation programmes on the incidence of cervical dysplasia is now evident in multiple countries.

6.4.4 Effectiveness in preventing recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis is a disease characterised by warty growths in the upper airway which may cause airway obstruction or voice change. Most are caused by HPV-6 and -11. A study reviewed 20 patients and vaccinated them with HPV4 as part of their treatment. All patients increased their inter-surgical intervals; this was most significant in males. Eight patients experienced complete remission and five partial remission.[114]

6.4.5 Duration of effectiveness

A 2014 systematic review of 10 RCTs, consisting of 46,436 vaccinated and control participants, and five observational studies investigated the effectiveness and short (average 3 years) or long-term (≥5 years, average 6 years) protection of HPV4 vaccine given to females aged 9-26 years when they were not sexually active or were negative for HPV-16 or 18 infection. Over the short-term, the pooled vaccine effectiveness for HPV infections prevented was 83% and 90% against persistent HPV infections. Effectiveness in preventing CIN2+ and CIN3+ lesions were 84% and 94% respectively. No loss of antiviral protection was observed over the long term against HPV-16 and -18, with 94% effectiveness in prevention of infection and 95% effectiveness in preventing persistent infections. Long-term effectiveness against CIN2+ lesions was 86%; there were no data for CIN3+. The quality of evidence was noted to be lower for long-term protection than the evidence for short-term protection.[2]

A review of long-term clinical efficacy of HPV vaccines summarised the available studies. For HPV4, naïve populations (females age 16-23 years and females and males aged 9-15 years) were evaluated for 5-8 years follow-up. No cases of CIN related to vaccine-type HPV were reported (efficacy 100%).[115] Summaries of HPV4 studies are given in Figure 7.

Study	Study subjects	Efficacy	Seropositivity	Follow-up
P007 (Villa et al[28])	Young women (age 16–23 years)	No cases of HPV 6/11/16/18-related CIN	Maintained up to 5 years	5 years
Nordic Study P015 (Nygard et al[29])	Young women (age 16–23 years)	No cases of HPV 6/11/16/18-related CIN	Trend up to 9 years	8 years
Extension P018 (Iversen[32])	Females and males (age 9–15 years)	No cases of HPV 6/11/16/18-related CIN	Maintained up to 8 years	6.8 years
Extension P019 (Luna et al[35])	Adult women (age 24–45 years)	One case of HPV 6/11/16/18-related CIN	Maintained up to 6 years	6 years
P020 (Giuliano et al[36])	Males (age 16–26 years)	Three cases of EGLs	–	3 years
P020 – AIN substudy (Palefsky et al[37])	Males – MSM (age 16–26 years)	Five cases of AIN due to HPV 6/11/16/18	–	3 years

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; EGLs, external genital lesions; AIN, anal intraepithelial neoplasia; MSM, men who have sex with men.

Figure 7. Long-term studies on quadrivalent vaccine (HPV4) – reproduced from De Vincenzo (2014)

6.4.6 Two-dose versus three-dose schedules

The effectiveness of two doses of HPV4 vaccine compared with three doses was evaluated in Denmark. The incidence of genital warts was compared within a cohort of over 550,000 girls. Of these, 374,248 (67.4%) had received HPV4 vaccine during October 2006 and December 2012. When comparing the crude incidence of genital warts with the number of vaccine doses, the study found that genital warts occurred significantly less frequently with each additional vaccine dose (unvaccinated 655 cases per 100,000; vaccinated with one dose 333 per 100,000; two doses 146 per 100,000; three doses 67.2 per 100,000; $p<0.001$ for each incidence rate ratio [IRR] comparing 1 vs 0, 2 vs 1 and 3 vs 2 doses). Taking in consideration changes in IRR due primarily to the effect of calendar time, the incidence rate remained significantly lower after three doses than two. When comparing the incidence of genital warts after two doses 2 months apart, the study found that genital wart incidence decreased by 27%, 45%, 55% and 63% when the timing between two doses was increased to 3, 4, 5 and 6 months, respectively. Three doses provided greater protection when the interval between dose 1 and 2 was short, the differences between two and three doses decreased when the time between the first two doses was longer. When the interval between dose 1 and 2 was

about 4 months, no significant difference in effect was seen for two or three doses, and at a 6-month interval, IRR was nearly 1. The overall pattern was the same for girls aged <16 and ≥16 years.[116] This supports the importance of affinity maturation in the role of protection.

A data linkage study in Australia compared the incidence of high and low grade CIN with the number of doses of HPV4 vaccine received. The study found that one, two or three doses of vaccine were associated with lower rates of CIN as long as the vaccine was given before screening commenced (indication of less sexual activity and lack of exposure to HPV). Even when measured within 5 years in a population that included those who were sexually active at the time of vaccination (as part of a catch-up campaign), fewer than three doses provided some protection against CIN. The youngest women had the strongest evidence of protection after partial doses, although high-grade CIN incidence in under 16-year olds was low and small numbers made estimates less precise.[117]

6.5 Summary of effectiveness

Given the variables that affect the impact of a vaccine programme, the reported impact from different countries varies. What is consistent is the clear positive association between vaccine coverage and impact.

Since the introduction of HPV vaccination programmes, there have been many studies documenting effectiveness and impact: over 130 studies on effectiveness in the period January 2013 to June 2016 are published.

The evidence for effect on HPV infection indicates a dramatic reduction in prevalence of vaccine-type HPV which is correlated with vaccine coverage in the population.

In countries with high HPV vaccine coverage, such as Australia and Denmark, there has been a profound reduction in the number of genital wart cases. However countries with more moderate coverage, such as NZ, have also observed significant reductions.

Declines in cervical dysplasia have now been reported and these are associated with the vaccine eligible cohorts.

Herd immunity has been observed and is evident for prevalence of infection, incidence of genital warts and cervical disease.

7 Age-specific issues and scheduling options

7.1 Background

Data from the NZ Youth 2007 survey suggested 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 were higher for Māori. Approximately 15% of sexually active students did not use or only sometimes used a condom.[118] 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.[119]

7.2 Objective

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

7.3 Review

7.3.1 Youth 2012

The Youth 2012 survey included adolescents aged between 12 and 18 years and 8,500 students took part of 12,503 invited.[120]

7.3.1.1 Sexual behaviours among NZ students

Of the Youth 2012 participants, 25% males and 24% of females reported ever having had sex. Of these, 18% of male students and 19% of female students reported being currently sexually active (sex in the last 3 months).

Among the sexually active participants, 44% had discussed the prevention of STIs with their partner and 46% reported using condoms all of the time. Seventeen percent reported they did not use or only sometimes used a condom, and this was associated with being younger and higher deprivation.[120]

7.3.1.2 Onset of sexual activity

Among Youth 2012 participants, 14.2% reported the onset of sexual activity had occurred by the age of 14 years. Of these 7.8% were aged 13 years or less. This excluded sexual abuse. By age 15 years, 24.3% of students had had sex. Of those reporting being currently sexually active, 5.6% were aged ≤13 years and 9.6% were aged 14 years.[120]

7.3.1.3 Sexual attractions

In the 2012 survey, 92% of students reported being exclusively attracted to the opposite sex (93% males and 91% females). A further 4% were attracted to the same-sex or both. The remaining 4% were unsure or attracted to neither sex.[120]

7.3.2 Optimal age for vaccination and scheduling options

As reviewed in 5.3.1, younger adolescents have a high antibody response to two doses of HPV vaccination, which is non-inferior to three doses in older adolescents and adults. In addition, effectiveness data indicates greater reductions in disease endpoints among the younger cohorts.

HPV vaccines are most effective in preventing infection when administered prior to exposure to HPV, and as demonstrated in pre-exposed women, that are unable to prevent precancer due to existing infection. Prior to the onset of sexual activity, young adolescents are less likely to have been exposed to HPV.

HPV9 provides a broader spectrum of protection prior to sexual debut, but still can protect against the types older adolescents and young adults have not been exposed to.

Another advantage of giving HPV9 as early as possible is that giving only two doses is likely to result in improved coverage. High coverage is correlated with herd effect and vaccine impact.

The duration of protection provided by HPV4 has been demonstrated to be long-lasting and follow-up studies have shown seropositivity to been maintained for at least 8-9 years[115]; it is expected that HPV9 will offer similar long-term protection.[57] However, there is insufficient long-term data to be certain whether or not vaccination in early adolescence is likely to wane by the age of 30 years.

7.4 Summary of age specific issues

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.

As immunogenicity is superior in younger adolescents making two dose schedules viable the administration of vaccine in early adolescence provides protection against acquisition of a broader spectrum of HPV types, is likely to improve coverage and consequently offer greater herd immunity.

Initial data provide optimism for the duration of protection and no waning in immunity has been observed for up to 9 years follow-up after HPV4 vaccination. Longer term data is anticipated from follow-up of pivotal trials, which will help to determine if those vaccinated in early adolescence will continue to be protected by the age of 30 years. The duration of protection of HPV9 is expected to be similar to HPV4.

8 International practices and other evidence around use

8.1 Objective

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

8.2 Review

HPV programmes differ by country.[94]

8.2.1 International practices

A summary of the countries that have included HPV vaccine in their National Immunisation programmes has been summarised by Garland et al (2016) and are presented from that report in Table 4.[94, 121]

Table 4. Supplemental table from Garland et al 2016, Countries Including HPV Vaccine in their National Immunization Programs (NIPs): Year Introduced, Target Age Groups, Delivery Method, and Coverage, 2006–2015

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
EUROPE						
Austria	2014	9-14		Schools/PC	62% for boys & girls (2015)	Recommendation begun in 2007; funding & 2-dose schedule started in 2014
Belgium	2007	12-13	13–18	Varies by region	Varies by region: 30%-83% (2012-2013)	Lower coverage in Flanders region, higher coverage in Wallonian region
Bulgaria	2012	12				
Czech Republic	2012	13		PC	65% (Unknown)	Reimbursed – no official NIP
Denmark	2009	12	13–15	PC/Health centres	82% (2015)	In August 2012 catch-up expanded to women up to 27 years
Finland	2013	11-12		Schools	68% (2015)	
France	2007	11-14	15–23	PC/Health centres	17% for 16 year olds (2014)	

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
Germany	2007	9-14		PC/Health centers	16- 56% (2012)	Coverage by age: 14yo - 16.3%; 15yo - 37.7%; 16yo - 45.9%; 17yo - 55.6%. Initial recommendation was for a vaccination age 12-17 years and 3-dose vaccination; STIKO recommendation since 2014 has been 2-dose vaccination for girls between the ages of 9–14 years.
Greece	2008	11-18		PC/Health centers	Varies by source: 5%-27% (2011)	
Greenland	2008	12	13–15	Mixed		
Hungary	2014	12		Schools	80% (2015) for 2-dose schedule	
Iceland	2011	12		Schools	88% (2014)	
Ireland	2010	12–13		PC/Health centers	85% for 12-13 yo, 45% for 18-19 yo (2014)	
Italy	2007–2008	12	Varies by region	PC/Health centers	11%-71% (2014)	Coverage by age: 11yo - 10.7%; 12yo - 62.4%; 13 yo - 67.0%; 14yo -71.1%; 15yo - 72.1%; 16yo - 70.9%; 17yo - 70.8%
Latvia	2010	12		Mixed	61% (2011)	
Liechtenstein		11-14	15-19			

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
Luxembourg	2008	12-18		PC/Health centers	29% (2008)	
Republic of Macedonia	2010	12	13–26	Schools	65% (2012)	
Netherlands	2010	12	13–16	Mixed	61% (2014)	
Norway	2009	12		Schools	79% (2014)	
Portugal	2009	13	17	PC/health centers	87% (2015)	
Romania	2010	12		Mixed	<5%	
San Marino	2009	11				
Slovenia	2009	12		Schools	49% (2012)	
Spain	2008	11–14		Varies by region	73% (2014)	
Sweden	2012	10–12	13-18	Schools	80% (2014)	
Switzerland	2008	11-14	15-19	Mixed	51% (2013)	
United Kingdom	2008	12–13	13–17	Schools	86% (2014)	

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
CENTRAL ASIA						
Uzbekistan (GAVI)	2015					
AMERICAS						
Argentina	2011	11		Mixed	50% (2013)	
Canada	2007–2009	9-14 for females in 4 provinces & 3 territories; 9-14 for females & males in 5 provinces	Varies by province	Schools	60 to 85% by region (2013)	
Barbados	2014	11				
Bermuda	2008	11-13				
Brazil	2014	9		Mixed		Also recommended in HIV+ population
Cayman Islands		11-13				
Chile	2015	9	11-12	Schools		Also recommended in HIV+ population
Colombia	2012	9-17		Mixed	87% (2013)	

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
Ecuador	2014	9		Clinics		
Guyana	2011	11				
Mexico	2008	10		Mixed	67%	Boys vaccinated in Mexico City
Panama	2008	10		Mixed	67% (2010)	
Paraguay	2013	10		Mixed		
Puerto Rico	2006	11-18 females & males				
Peru	2011	10		Schools		
Surinam	2013	9				
Trinidad & Tobago	2013	11-12				
United States	2006	11–12 females & males (starting in 2011)	13–26	PC/Health centers	40% for females, 22% for males, (2014)	
Uruguay	2013	12		Clinics (permissive)		

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
ASIA-PACIFIC						
Australia	2007	12-13 females & males (from 2013)	Up to 26 to end of 2009 (females) 14-15 year old catchup (males) (2013-14)	Schools	73.1% girls (2014) Slightly lower for boys	
Bhutan	2010	12	13–18	Mixed	>90% (2014)	
Brunei	2012-2015	12-13				
Malaysia	2010	13	13–18	Schools	87% (2011)	
Japan	2011	13		Health Centers	0.6% (2014 - Sapporo)	
Philippines	2015	9		Health Centers		
WESTERN PACIFIC						
Fiji	2008	13				
Kiribati	2011	NA				
Federated States of Micronesia	2009	9		PC/Health centers		

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
Marshall Islands	2008	11-12		PC/Health centers		
New Zealand	2008	12	13–18	Mixed [j]	56% (2014)	
Palau	2009	9-26		PC/Health centers		
Singapore	2010	9–26		PC/Health centers		
EASTERN MEDITERRANEAN						
Abu Dhabi, United Arab Emirates	2008	15–17	18–26	Schools	59% (2011)	
Israel	2011 (females) & 2015 (males)	14 (females & males)		Schools/Health centers	~60% (2014)	
AFRICA						
Botswana	2015	9-13		Schools/Health centers		2-dose program; 3 doses for HIV positives
Lesotho	2012	9-13				
Libya	2013	15				

Region/Country	Year Introduced into NIP[1]	Target Age Group (Years) or Grade [b 1]	Catch-up Age Group (Years)[2]	Delivery for Primary Target Group[2]	Estimated 3-dose Coverage [c] (year evaluated)[2]	Comments
Rwanda (GAVI)	2011	PG 6	In year 2 & 3, PG 6 & SG 3 (9th school year)	Schools [k]	99% (2013)	
South Africa	2014	9 (PG4)		Schools	87% (Dose 1)	
Republic of Seychelles	2014	10-12		Schools		
Uganda (GAVI)	2012	10		Schools		

Abbreviations: PG – primary school grade; SG – secondary school grade; PC – primary care providers; NA – not available; Mixed – schools plus primary care and health centres; yo – years old;

[b] Target age group in years

[c] Data obtained from published data, official websites, or personal communication. Data were not available for all countries; different methods were used to evaluate vaccine coverage; comparisons between countries are not possible (see appendix 2 of supplemental data for further details on data sources)

Table updated from Markowitz L, Tsu V, Deeks SL et al. *Vaccine* 305 (2012): F139-F148 and Bruni L, Barrionuevo-Rosas L, Albero G et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in the world. Summary Report 2015-12-23.

8.2.1.1 Australia

Australia initially introduced HPV4 freely to females 12-26 years of age and achieved high coverage very quickly. The programme from April 2007 to December 2009 used school-based delivery for girls aged 12–18 years. From July 2007 to December 2009, general practitioners and other community providers provided the vaccine to ≤26 years. Since 2009, routine HPV vaccination has continued for girls in the first year of high-school (age 12–13 years) as part of the National Schedule. In February, 2013, the program was expanded to include boys aged 12–13 years, with a catch-up for ages 14–15 years up to December 2014.

8.2.1.2 United States

The United States licensed HPV4 in June 2006 and the Advisory Committee on Immunization Practices (ACIP) recommended a routine three-dose schedule for females aged 11 or 12 years with catch-up for those aged 13 to 26 years. In October 2009, the recommendation was updated to include males aged 9 to 26 years. In 2011 the vaccine was routinely recommended in aged 11 and 12 males, with catch-up in males aged 13 to 21 years.

8.2.1.3 European countries

In Sweden, partially subsidised opportunistic vaccination began in October 2006 for girls ages 13-17 between May 2007-2011. Girls and women outside this target age range could receive the vaccine but were not eligible for reimbursement. In 2012 a school-based program using HPV4 was implemented. Girls aged 10-12 are receive three doses through school health services, with catch-up third dose offered to girls ages 13-18.

In Belgium, HPV vaccines started to be reimbursed in 2007 for certain cohorts in some regions. Full reimbursement began December 2008 for all females aged 12 to 18 years.

HPV vaccination was initially recommended in France in 2007 for 14 year old females (primary cohort) and for those aged 15–23 years old (as catch-up) who had never had sexual intercourse or within the first year following sexual debut. French recommendations were updated in September 2012, and HPV vaccination is now recommended in adolescent girls age 11 to 14 years (primary cohort), with a catch-up for those aged 15–19 years.

8.2.1.4 Canada, Ontario

Ontario offered a three-dose schedule, free-of-charge, to all grade 8 girls in September of 2007. Delivery is through school-based immunisation clinics, but girls also may receive the vaccine from primary care or at their health unit freely. Before September 2012, eligible girls had until the end of their grade 8 year to initiate the vaccine series and until the end of grade 9 to complete it. During the study period, girls who were not eligible for the school-based program (e.g., in grade 8 before 2007) could obtain the vaccine series for approximately $400.

8.2.2 Maternal vaccination

While rare, juvenile-onset laryngeal papilloma is caused by intrapartum or perinatal transmission of HPV-6 and -11. Neutralising HPV antibodies are transferred transplacentally to the fetus. The presence of these antibodies is expected to offer protection to the newborn against the establishment of HPV-6 and -11 infection.[122, 123] Further data is required to determine a benefit of vaccinating mothers during pregnancy and providing protection to infants of mothers with genital warts.

8.3 Summary of other evidence around use

Internationally, HPV vaccination is offered in school and health-care centre settings between the ages of 9 and 18 years. Some countries have introduced immunisation of males and females, whilst others only provide vaccine for girls. As of 2014/2015, for many countries, coverage was highly variable with the highest around 87% for three doses.

Maternally transferred HPV antibodies may provide protection to infants from juvenile-onset laryngeal papilloma and recurrent respiratory papillomatosis.

9 References

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