NONAVALENT HPV VACCINE
(GARDASIL 9)

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DISCLOSURE

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EXECUTIVE SUMMARY

Background

Cervical cancer is ranked as fourth most frequently diagnosed cancer worldwide and the fourth leading cause of cancer death in women. According to the most recent Malaysian National Cancer Registry Report, the age-standardized rate of cervical cancer is 7.8 per 100,000 females. Based on Malaysia HPV types prevalence study in 2017, overall prevalence of HPV infection in Malaysia's multi-ethnic population was 7.2% whereby 6.5% being high-risk genotypes. Recent study reported that the most common HPV infections in Malaysia were caused by HPV16 (35.7%), HPV18 (26.0%), HPV58 (9.1%), HPV33 (7.1%), HPV 31 (1.9%), HPV 45 (1.9%) and HPV 52 (1.3%). However, data for HPV 6 and HPV 11 were not available.

In developed countries, vaccination programmes are in place which enable girls to be vaccinated against HPV and women to get screened regularly. Screening allows pre-cancerous lesions to be identified at stages when the lesions can easily be treated. Early treatment prevents up to 80% of cervical cancers in these countries. Meanwhile in developing countries, there is limited access to these preventive measures and cervical cancer is often not identified until it has further advanced and symptoms developed.

Thus, the WHO recommended a comprehensive approach to cervical cancer prevention and control. The recommended set of actions includes interventions across the life course, on of it is vaccination. It should be multidisciplinary, including components from community education, social mobilization, vaccination, screening, treatment and palliative care. In 2011, one technology review (TR) was conducted by Malaysian Health Technology Assessment Section (MaHTAS) on bivalent (2vHPV) and quadrivalent (4vHPV) vaccine. Both vaccines were focused to be effective for specified HPV types (6, 11, 16 and 18), however, there was concerned on the safety profile. In February 2015, the Advisory Committee on Immunization Practices (ACIP) included the nonavalent HPV (9vHPV) vaccine in its recommendation for routine HPV vaccination of pre-adolescent aged 11 or 12 years, female aged 13 to 26 years and males aged 13 to 21 years who had not previously received bivalent HPV vaccine or quadrivalent HPV vaccine.

Since the approval of nonavalent HPV vaccine, Ministry of Health (MOH) is planning to improve the vaccination program in Malaysia. Thus, the Head of Vaccine Preventable Disease / Food & Water Borne Disease Sector, Disease Control Division, MOH requested the technology review in order to look at the effectiveness, safety and cost-effectiveness of nonavalent HPV vaccine compared to quadrivalent and bivalent HPV vaccines in prevention of cervical cancer in female-only vaccination program and whether the added benefit of nonavalent HPV vaccine worth the investment? The requestor also would like to assess whether the upgrading of vaccination program from female-only vaccination to universal vaccination program using the nonavalent HPV vaccine will it be more cost-effective compared to current practice (female-only vaccination with bivalent or quadrivalent HPV vaccines.

Objective/aim
To assess the safety, efficacy/effectiveness and cost-effectiveness of nonavalent HPV vaccine compared to bivalent or quadrivalent HPV vaccine.

Results & Conclusion
The included studies consisted of seven systematic reviews (SR), three RCT and one cost analysis study. Those studies were conducted in Brazil, Netherlands, Italy, Norway and Australia. The study populations were all over the world including European country, USA and Asia.

Efficacy / Effectiveness

i. Infections Risks

Among non-HPV infected populations (female aged 16 to 26 years old), nonavalent HPV vaccine was highly effective in reducing diseases related to HPV types that were covered by the nonavalent HPV vaccine. Compared with quadrivalent HPV vaccine, there was no cases of cervical disease, vulva disease or vaginal disease related to HPV 31, 33, 45, 52 and 58 were detected in nonavalent HPV vaccinated group. Furthermore, HPV-52 and 58 related infections were most frequent in all countries with quadrivalent HPV vaccination.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the overall prevalence of HPV types 16 and 18 in girls aged 13 to 19 years old was significantly decreased compared with in women aged 20 to 24 years old. However, for HPV types 31, 33, 45, 52 and 58 and non-high-oncogenic risk, the overall prevalence was not significantly changed. In high-female vaccination coverage, anogenital warts was significantly reduced in girls and boys15 to 19 years old, and women 20 to 35 years old women.

ii. Immunogenicity and Non-Inferiority

Within one to seven month, the nonavalent HPV vaccine successfully seroconverted with high GMTs level for all the HPV types covered. Compared with quadrivalent vaccine, the immunogenicity and non-inferiority response was similar for HPV 16, 18, 6 and 11. In terms of age, the GMTs level decreased as the age increased; the GMTs level for all HPV types covered by nonavalent HPV vaccine was higher in girls and boys aged nine to 15 years old than in women aged 16 to 26 years old. Among Asian populations, Indian females showed highest GMTs level than other races.

Concomitant administration of nonavalent HPV vaccine with MCV4 vaccine, Tdap vaccine and polio vaccine showed positive results as non-concomitant group. The nonavalent HPV vaccine was successfully seroconverted with elevated GMTs for all HPV types covered by the vaccine. Meanwhile, the immune response for other vaccine; diphtheria, tetanus, all pertussis and polio antigen were also established.

Girls and boys aged nine to 14 years old receiving the two doses of nonavalent HPV vaccine was non-inferior to a three doses nonavalent HPV vaccine in adolescent girls and young women aged 16 to 26 years old.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the seroconversion was significantly higher for both HPV types 16 and 18.

iii. Vaccination Coverage

Strong herd effects were expected from vaccinating girls-only at 40% coverage or even with coverage as low as 20%. Besides that, with high female-vaccination coverage (70% to 80%), the anogenital warts were significantly reduced by 32% in women (age of 20 to 39 years old) and boys (age of 15 to 19 years old). On the other hand, additional boys in girls-only vaccination just resulted in small increment in relative reduction prevalence ($RR_{prev)}$ in both women and men.

Overall, the prevalence of HPV types 16 and 18 were significantly reduced in girls aged 13 to 19 years old and not significantly reduced in women aged 20 to 24 years old. However, the association of dose response and vaccination coverage was significant in the women group compared to the girl's group. Although, the prevalence of HPV types 31, 33, 45, 52 and 58 was significantly reduced in girls (aged 13 to 19 years old), no significant association between dose response and vaccination coverage were observed.

Safety

Based on above review, the adverse events were more common in nonavalent HPV vaccine compared to quadrivalent HPV vaccine. The most common AEs were fever, pruritus, GI symptom and injection-site related AEs. There was also small number of serious AEs reported which more cases were occurred in nonavalent HPV vaccine than quadrivalent vaccine. However, the SAEs was not described in detail. There were no death-related to the HPV vaccine reported.

By gender, more adverse events occurred among females than male's population. The adverse events were also more common in concomitant vaccination compared to non-concomitant vaccination.

Cost / Cost-Effectiveness

The SR of cost-effectiveness included studies published (2014-2016) concluded that if the HPV vaccination coverage for female was above 75%, gender neutral vaccination was less cost-effective than when targeting only girls aged nine to 18 years. The multi cohort immunisation strategy was cost-effective in the age range nine to 14 years but the upper age limit which vaccination were no longer cost-effective needs further assessment. Furthermore, there was inconclusive evidence to proof greater cost-effectiveness of nonavalent HPV vaccine compared to the quadrivalent or bivalent HPV vaccine as the price for nonavalent HPV vaccine was still uncertain.

One cost-effectiveness study conducted in Italy showed that switching from the quadrivalent HPV vaccine to the nonavalent HPV vaccine girls-only vaccination was cost-effective. Although there was a local cost-effectiveness study conducted, however, no full-text article was retrieved. Financial implication of using nonavalent HPV vaccine in national HPV-vaccination programme was conducted. The difference from the current national HPV-vaccination programme to nonavalent HPV-vaccination programme is expected approximately >90% increase in expenditure. Overall, the cost-effectiveness of nonavalent HPV vaccine in Malaysia was inconclusive with potentially high budget implication.

Methods

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane

Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 5 August 2019. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

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1. BACKGROUND

Cervical cancer is ranked as fourth most frequently diagnosed cancer worldwide and the fourth leading cause of cancer death in women. Incidence data from GLOBOCAN database indicate that a total of 18.1 million new cancer cases were diagnosed in year 2018, with an estimated 570,000 cervical cancer cases and 311,000 deaths was caused by cervical cancer.[1] Up to 2018, more than 200 types of HPV have been identified, and about 15 types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, -82) have been shown to cause cervical cancer.[2] According to the most recent Malaysian National Cancer Registry Report, the age-standardized rate of cervical cancer is 7.8 per 100,000 females. Based on Malaysia HPV types prevalence study in 2017, overall prevalence of HPV infection in Malaysia's multi-ethnic population was 7.2% whereby 6.5% being high-risk genotypes.[3] Recent study reported that the most common HPV infections in were Malaysia caused by HPV16 (35.7%), HPV18 (26.0%), HPV58 (9.1%), HPV33 (7.1%), HPV 31 (1.9%), HPV 45 (1.9%) and HPV 52 (1.3%). However, data for HPV 6 and HPV 11 were not available.[4]

According to World Health Organisation (WHO), it takes 15 to 20 years for cervical cancer to develop in women with normal immune systems. However, it can take only 5 to 10 years in women with weak immune systems. In developed countries, vaccination programmes are in place which enable girls to be vaccinated against HPV and women to get screened regularly. Screening allows pre-cancerous lesions to be identified at stages when the lesions can easily be treated. Early treatment prevents up to 80% of cervical cancers in these countries. Meanwhile in developing countries, there is limited access to these preventive measures and cervical cancer is often not identified until it has further advanced and symptoms developed. In addition, access to treatment of such late-stage disease (for example, cancer surgery, radiotherapy and chemotherapy) may be very limited, resulting in a higher rate of death from cervical cancer in these countries. Thus, the high mortality rate from cervical cancer globally could be reduced by effective interventions.[5]

Thus, the WHO recommended a comprehensive approach to cervical cancer prevention and control. The recommended set of actions includes interventions across the life course. It should be multidisciplinary, including components from community education, social mobilization, vaccination, screening, treatment and palliative care. There are three stages of cervical cancer prevention; primary prevention which consist of HPV vaccination of girls before they become sexually active (aged nine to 14 years old, secondary prevention for women who are sexually active where they should be screened for any abnormal cervical cells and tertiary prevention for treatment of invasive cancer at any age and palliative care.[5]

The HPV vaccine has been included in the Vaccine for Children (VFC) program since 2006.[6] In 2011, one technology review (TR) was conducted by Malaysian Health Technology Assessment Section (MaHTAS) on bivalent (2vHPV) and quadrivalent (4vHPV) vaccine. Both vaccines were focused to be effective for specified HPV types (6, 11, 16 and 18), however, there was concerned on the safety profile.[7] Meta-analyses in 2018 also showed that both bivalent and quadrivalent vaccine were effective in

prevention of HPV 6, 11, 16 and 18 which were responsible for cervical intraepithelial neoplasia 1, 2 and 3 (CIN1, CIN2 and CIN3).[8]

In February 2015, the Advisory Committee on Immunization Practices (ACIP) included the nonavalent HPV (9vHPV) vaccine in its recommendation for routine HPV vaccination of pre-adolescent aged 11 or 12 years, female aged 13 to 26 years and males aged 13 to 21 years who had not previously received bivalent HPV vaccine or quadrivalent HPV vaccine. The nonavalent HPV vaccine is also recommended for men who have sex with men, immunocompromised persons and those with HIV infection. For instance, the nonavalent HPV vaccine is licensed in the United State of America (USA) in women up to age 26 years, in Australia and Canada up to age 45 years and in EU without upper age limit.[9]

The implementation of HPV vaccination program varies across the countries and most of the countries recommend HPV vaccination for at least one cohort of adolescent or pre-adolescent girls (starting from nine years of age). The catch-up programs were extended to older girls and women and have been implemented in nine European countries, USA and Canada. Recently, few countries, including USA, extended the HPV vaccine recommendation to the male population as well.[10]

Since the approval of nonavalent HPV vaccine, Ministry of Health (MOH) is planning to improve the vaccination program in Malaysia. Thus, the Head of Vaccine Preventable Disease / Food & Water Borne Disease Sector, Disease Control Division, MOH requested the technology review in order to look at the effectiveness, safety and cost-effectiveness of nonavalent HPV vaccine compared to quadrivalent and bivalent HPV vaccines in prevention of cervical cancer in female-only vaccination program and whether the added benefit of nonavalent HPV vaccine worth the investment? The requestor also would like to assess whether the upgrading of vaccination program from female-only vaccination to universal vaccination program using the nonavalent HPV vaccine will it be more cost-effective compared to current practice (female-only vaccination with bivalent or quadrivalent HPV vaccines.

2. OBJECTIVE/AIM

To assess the safety, efficacy/effectiveness and cost-effectiveness of nonavalent HPV vaccine compared to bivalent or quadrivalent HPV vaccine.

3. TECHNICAL FEATURES

3.1 Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted infection and skin-to-skin genital contact is sufficient for virus transmission.[2] Figure 1 shows the image of HPV.

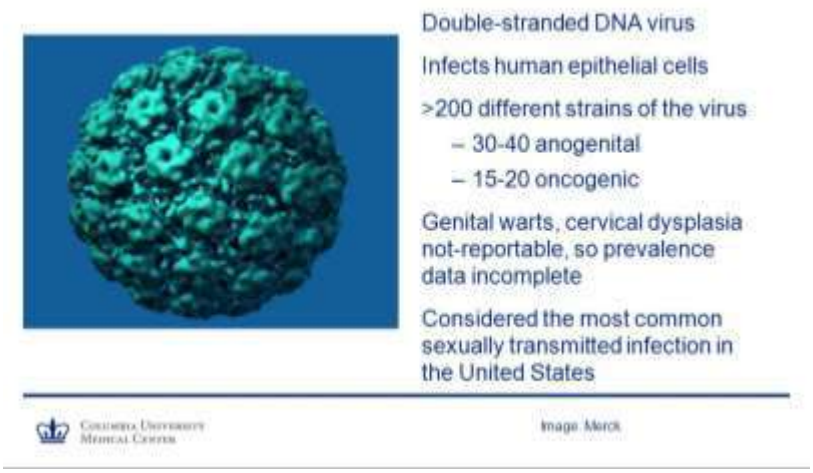

Figure 1: Human Papillomavirus (HPV)

3.2 Human papillomavirus (HPV) Vaccine

Currently, there are three HPV vaccines available. Those are listed below and table 1: -

i) Quadrivalent vaccine (Gardasil): First HPV vaccine to be authorized by the European Medicines Agency (EMA) in September 2006 for the European Union. The vaccine was constituted by an L1 surface antigen of the human papilloma viruses. Gardasil is a quadrivalent VLP (virus like particles) vaccine consisting of serotypes 6, 11, 16 and 18, adjuvanted with AAHS aluminum salts (amorphous aluminum hydroxyphosphate sulphate).[2]

ii) Bivalent vaccine (Cervarix): Second HPV vaccine to be authorized in 2007. The vaccine was constituted by an L1 surface antigen of the human papilloma viruses. Cervarix is a bivalent VLP vaccine consisting of serotypes 16 and 18, adjuvanted with aluminum salts $AS0_4$ $(Al(OH)_3)$.[2] There were studies showed bivalent vaccine had cross-protective effects towards HPV type 31, 33 and 45.[11]

iii) Nonavalent vaccine (Gardasil 9): European Medicines Agency (EMA) authorized marketing of the Gardasil 9 vaccine in the European Union on 10th of June 2015. Gardasil 9 consists of serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58, with a double adjuvant dose compared to Gardasil in order to extend the spectrum of protection.[2]

The WHO recommends the HPV vaccination (any HPV vaccine) for girls in the age group of nine to 13 years old. Girls who receive first dose of HPV the vaccine before age of 15 years can use a two-dose schedule. The interval between the two doses should be six months. There is no maximum interval between the two doses; however, an interval of no greater than 12 to 15 months is suggested. If the interval between doses is shorter than five months, then a third dose should be given at least six months after the first dose. Meanwhile, for immunocompromised individuals, including those who are living with HIV, and females aged 15 years and above, they require three doses of HPV vaccine (at 0,1-2 and 6 months' schedule) to be fully protected. Each dose consists of 0.5 ml HPV vaccine administered through intramuscular.[12]

Table1: Basic Information on the Globally Licensed Human Papillomavirus Vaccines

	2vHPV (Cervarix®)	4vHPV (Gardasil®)	9vHPV (Gardasil 9®)
Vaccine vial image			
Manufacturer Expression system	GlaxoSmithKline Baculovirus	Merck and Co., Inc. Yeast	Merck and Co., Inc. Yeast
	(*Trichoplusia ni* insect cell)	(*Saccharomyces cerevisiae*)	(*Saccharomyces cerevisiae*)
HPV types	16/18	6/11/16/18	6/11/16/18/31/33/45/52/58
VLPs protein (μg)	20/20	20/40/40/20	30/40/60/40/20/20/20/20/20
Adjuvants	500 μg aluminum hydroxide, 50 μg	225 μg amorphous aluminum	500 μg amorphous aluminum
	3-O-desacyl-4' monophosphoryl lipid A	hydroxyphosphate sulfate	hydroxyphosphate sulfate
Volume per dose	0.5 mL	0.5 mL	0.5 mL
Dosing regime	0, 1, 6 month	0, 2, 6 month	0, 2, 6 month
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Approval time by FDA	October, 2009	June, 2006	December, 2014

1. The information of Cervarix® is available from http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf;
2. The information of Gardasil® is available from http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf;
3. The information of Gardasil 9® is available from http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf;
(Accessed on 20 April 2017)

3.2.1 Mechanism of Action Human Papillomavirus Vaccine

The exact mechanisms of action of the HPV vaccines are unknown. Current hypotheses were based on data from animal studies demonstrating the naive animals passively immunized with purified serum immunoglobulin G (IgG) from either virus-like particle (VLP) immunized or naturally-infected animals were completely protected against high dose of viral challenge. Theoretically, the VLPs were rapidly bound by myeloid dendritic cells (DCs) and B lymphocytes and signal via Toll-Like Receptor (TLR)-dependent pathways essential for B-cell activation and antibody generation. The protection was thought to be due to direct action of serum antibodies transudate and exudate to the site of infection at the cervix. However, level of antibody required for protection was unknown.[13]

3.2.2 Malaysia's HPV Vaccination Program

In Malaysia, free vaccination was offered to school girls in secondary school which is usually at the age of 13 in the index year. The national programme on HPV immunisation was started in 2010 with either bivalent or quadrivalent HPV vaccine. With strong collaboration with a range of stakeholders included Ministry of Education, within two years the programme achieved the target of vaccinating about 250,000 13 years old school girls each year. Estimated population vaccination-coverage for the full vaccine course, considering also those not in school, was estimated at 83% to 91% per year. [14-15]

4. METHODS

4.1. Searching

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS

Economic Evaluation Database, and Embase 1996 to 5 August 2019. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieved articles.

Appendix 1 showed detailed of the search strategies.

4.2. Selection

Only one reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the eligibility of the selected full-text articles for final selection.

The inclusion and exclusion criteria were:

Table 2: Inclusion Criteria

Inclusion criteria	
Population	Human papillomavirus, cervical cancer
Interventions	Human papillomavirus vaccine, nonavalent HPV vaccine, 9-valent HPV vaccine
Comparators	Bivalent vaccine, 2-valent HPV vaccine, cervarix, quadrivalent vaccine, 4-valent HPV vaccine, gardasil
Outcomes	Effectiveness and efficacy, safety and cost-effectiveness
Study design	Systematic review (SR), SR and meta-analysis (MA), randomised controlled trial (RCT)
	English full text article

Table 3: Exclusion Criteria

Exclusion criteria	
Study design	Animal studies, laboratory studies, case reports, case series
Intervention	Other than HPV vaccine
Outcome	Non-medical condition
	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP), Cochrane tools, and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2). Data were extracted from included studies using a pre-designed data extraction from (evidence table as shown in Appendix 3) and presented in tabulated format with narrative summaries. No Meta-analysis was conducted for this review.

5. RESULTS AND DISCUSSION

A total of 7,861 titles were screened and after removing duplications and studies from 1980s and 1990s, 1,586 abstracts were screened. Out of 1,586 abstracts, 1,511 studies were excluded because of not meeting the inclusion criteria. Twenty-five full texts studies were assessed for eligibility. Out of 25 studies, eleven studies were included in the report; nine on the effectiveness and safety and two studies on cost-effectiveness.

The included studies consisted of seven systematic reviews (SR), and three RCT and one cost analysis study. Those studies were conducted in Brazil, Netherlands, Italy, Norway and Australia. The study populations were all over the world including European

country, USA and Asia. The characteristics of included studies were discussed in the next section. Figure 2 shows the flow chart of the study selection.

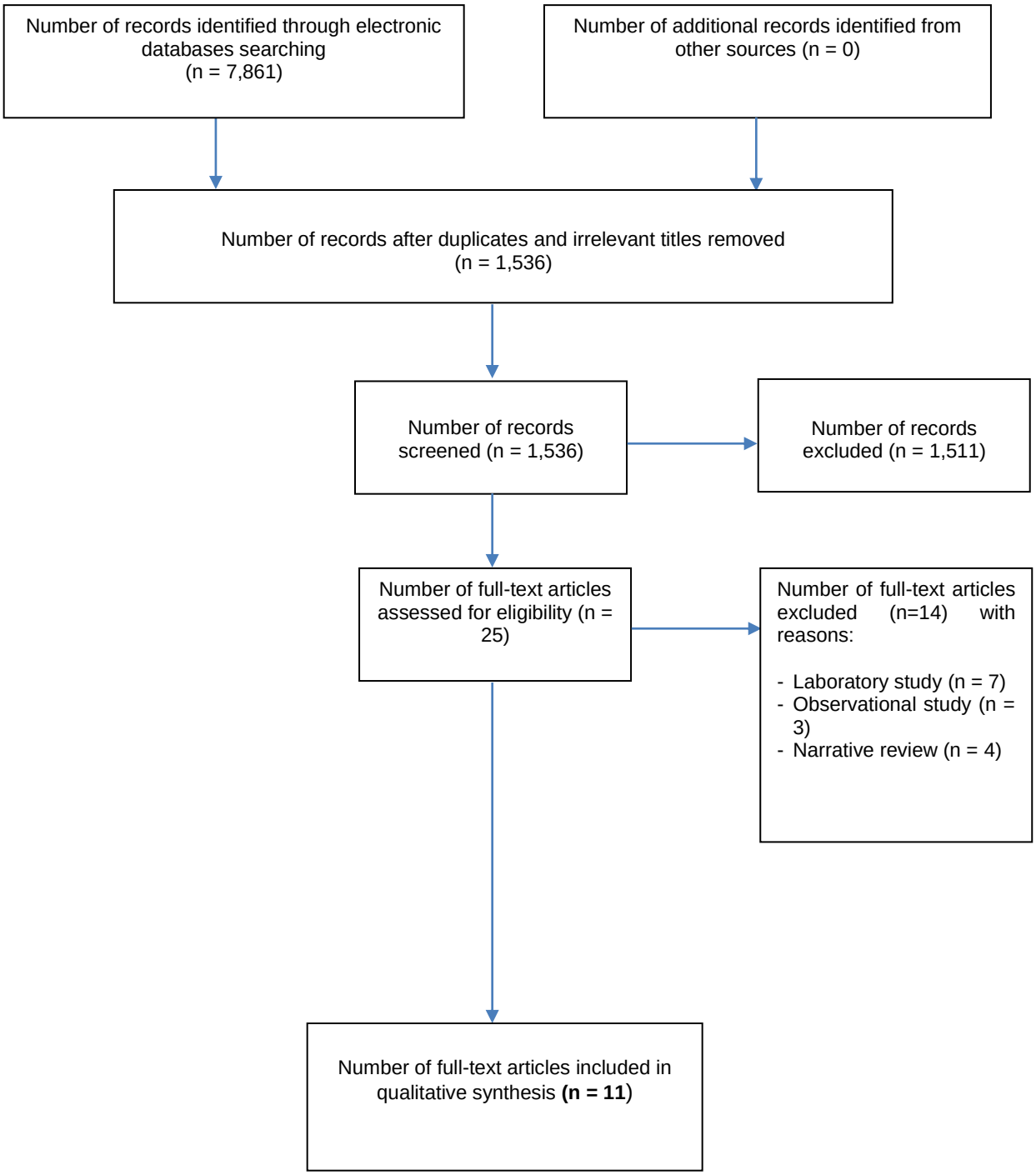

Figure 2: Systematic Search of HPV Vaccine

5.1 RISK OF BIAS

One of the tools that are being used by MaHTAS to assess the risk of bias is the CASP checklist which consists of eight critical appraisal tools designed for SR, RCT, cohort studies, case control studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rule. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The assessment of the risk of bias showed that, the included studies comply the assessment criteria.

The results of risk of bias of included studies are summarised in table 4 and table 5.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Signorelli C et al 2017	+	+	+	+
Setiawan D et al. 2017	+	+	+	+
Brisson M et al. 2016	+	+	+	+
Drolet M et al. 2015	+	+	+	+
Costa APF et al. 2017	+	+	+	+
Moreira JR et al. 2016	+	+	+	+

Figure 3: Assessment of risk of bias of Systematic Review (CASP)

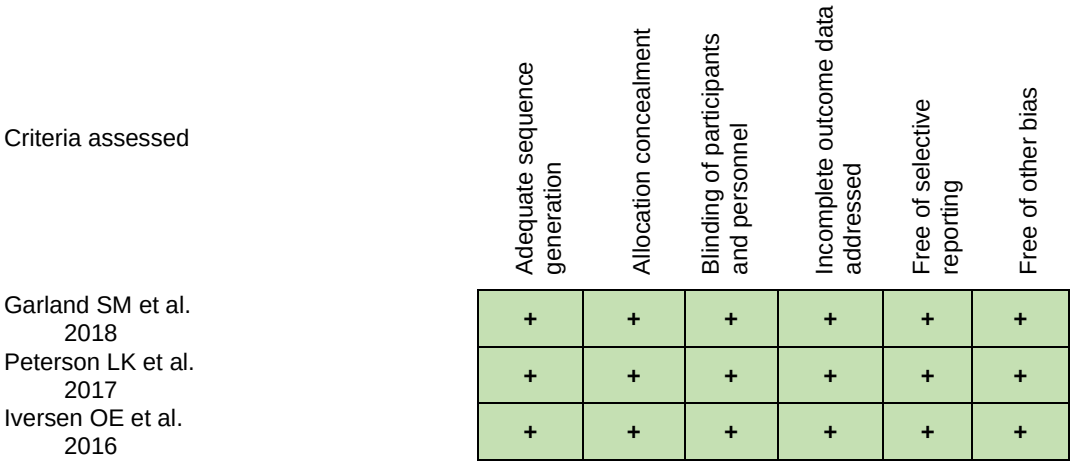

Figure 4: Assessment of risk of bias of RCT (Cochrane)

Study Population

Most of the included studies involved population from several clinical trials and some studies analyse similar clinical trials. Some of the populations were listed in table 4.

Table 4: Study Population of Included Studies

Included Studies	Clinical Trial	Description
Garland SM et al. 2018	Study 001 (NCT00543543)	(N = 13,598) Young women aged 16 to 26 years of age with 9-valent HPV vaccine (n=6,799) versus women of same age with 4-valent HPV vaccine (n = 6,799)
	Study 002 (NCT00943722)	2,604 girls and boys aged nine to 15 years compared with young women aged 16 to 26 years, across 72 sites in 17 countries
Signorelli et al. 2017	Study 001 (NCT00543543)	(N = 13,598) Young women aged 16 to 26 years of age with 9-valent HPV vaccine (n=6,799) versus women of same age with 4-valent HPV vaccine (n = 6,799)
	Study 002 (NCT00943722)	2,604 girls and boys aged nine to 15 years compared with young women aged 16 to 26 years, across 72 sites in 17 countries
	Study 005 (NCT00988884)	(N = 3,074) Virginal girls and boys aged 9 to 15 years with 9-valent HPV vaccine (n = 2,604) versus women age 16 to 26 years with 9-valent HPV vaccine (n = 470)
	Study 007 (NCT01073293)	(N = 1,241) Virginal girls and boys aged 11 to 15 years with concomitant arm (n = 621) versus girls and boys with non-concomitant arm (n = 620) (Nonavalent HPV vaccine and MCV4 and Tdap vaccine)
Peterson LK et al. 2017	Study 001 (NCT00543543)	(N = 13,598) Young women aged 16 to 26 years of age with 9-valent HPV vaccine (n=6,799) versus women of same age with 4-valent HPV vaccine (n = 6,799)
	Study 002 (NCT00943722)	(N = 3,074) Virginal girls and boys aged 9 to 15 years with 9-valent HPV vaccine (n = 2,604) versus women age 16 to 26 years with 9-valent HPV vaccine (n = 470)
	Study 005 (NCT00988884)	(N = 1,241) Virginal girls and boys aged 11 to 15 years with concomitant arm (n = 621) versus girls and boys with non-concomitant arm (n = 620)

Included Studies	Clinical Trial	Description
		(Nonavalent HPV vaccine and MCV4 and Tdap vaccine)
	Study 007 (NCT01073293)	(N = 1,054) Virginal girls and boys aged 11 to 15 years with concomitant arm (n = 526) versus girls and boys with non-concomitant arm (n = 528) (Nonavalent HPV vaccine and diphtheria, tetanus, pertussis and poliomyelitis vaccine)
	Study 009 (NCT01304498)	(N = 600) Virginal girls and boys with 9-valent HPV (n = 300) versus girls and boys with 4-valent HPV (n = 300)

5.2. EFFICACY/ EFFECTIVENESS

Efficacy and effectiveness of nonavalent HPV vaccine will be based on the outcomes of the vaccine which were the infection risks (cervical disease, vulvar disease or vaginal disease related to HPV-31/33/45/52/58 and anogenital wart) and immunogenicity which included the vaccine non-inferiority (Geometric Mean Titre [GMT] and seroconversion rate [SCR]).

5.2.1 Infection Risks

The studies assessed the risk of diseases development after HPV vaccination. Those diseases were high-grade cervical disease, vulva disease, vaginal disease incidence and anogenital warts.

Nonavalent HPV Vaccine

The SR by Signorelli C et al. (2017) included ten studies which consists of eight different trials. No meta-analyses were performed due to studies heterogeneity in study design, tested interventions and comparator and targeted study population. The study compared nonavalent HPV vaccine with quadrivalent HPV vaccine. The authors underwent modified intention-to-treat (ITT) populations for Study 001 (refer table 4). The included subjects were both not HPV-infected and HPV-infected at the time of vaccination, who received at least one dose of vaccine and the analysis showed that high-grade cervical, vulva and vaginal disease incidence were similar in nonavalent HPV vaccine and quadrivalent HPV vaccine; irrespective of HPV testing results (14.0 per 1000 person-years, risk reduction = 0.7, 95% CI -15.7, 14.8). When restricting analysis to those not HPV-infected participants at the time of vaccination, the nonavalent HPV vaccine risk reduction was 42.5% (95% CI 7.9, 65.9), which reduced 100% (95% CI 70.4, 100) when only disease related to HPV types which was covered under nonavalent HPV vaccine were considered. Then on per protocol population; the nonavalent HPV vaccine efficacy to be ≥96% for all considered clinical outcomes related to HPV types 31, 33, 45, 52 or 58 as well as persistent infection (≥6 month's duration).[16, level 1]

In RCT by Garland SM et al. (2018); Study 001 (refer table 4) showed that nonavalent HPV vaccine prevented HPV 31/33/45/52/58-related persistent infections after ≥ 6 months and ≥ 12 months in Asian participants with an efficacy of 95.8% (95% CI 87.8, 98.9) and 93.9% (95% CI 81.4, 98.4) respectively. In ≥ 12 months' period no cervical disease, vulvar disease or vaginal disease related to HPV-31/33/45/52/58 were reported. The nonavalent HPV vaccine also reduced the risk of HPV-31/33/45/52/58-related cervical cytological abnormalities by 92.1% (95% CI 71.5, 98.7). The incidence of HPV-31/33/45/52/58-related cervical biopsies was also reduced by 100% (95% CI 73.4, 100). However, in participants who received quadrivalent HPV vaccine; HPV-52 and HPV-58

related persistent infections were most frequent in all countries. The nonavalent HPV vaccine demonstrated efficacy against persistent infection related to HPV-52 or HPV-58 among participants from Hong Kong/Taiwan, Japan and Thailand. However, no cases of HPV-52/58- related persistent infection were observed in the nonavalent HPV vaccine group from South Korea. The nonavalent HPV vaccine also prevented HPV-31/33/45/85/58-related persistent (≥ 12 months) infections with an efficacy of 93.9% (95% CI 81.4, 98.4) in Asian participants. No cases of cervical, vulvar or vaginal disease related to HPV-31/33/45/52/58 were detected in the nonavalent HPV vaccination group, compared with seven cases of cervical disease in quadrivalent HPV vaccine (four in Hong Kong/Taiwan, two in Japan and one in Thailand).[17, level 1]

Vaccination Programme (Quadrivalent and Bivalent HPV Vaccine)

Drolet M et al. (2015) conducted a SR and MA to summarise existing evidence about population-level effect of HPV vaccination, as measured in time-trend studies in girls and young women targeted for vaccination and in boys, men and older women. There were 20 included studies; seven on HPV infection, eleven on anogenital warts and two on high-grade cervical lesions. The overall total participants were 16,600 women with more than 125 million person-years of follow-up for anogenital warts and 15 million female-years of follow-up for high-grade cervical lesions. All of the studies included used either quadrivalent HPV vaccine or bivalent HPV vaccine and was conducted in nine high income countries (USA, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada and Germany). The primary outcome of the SR was relative risk (RR) comparing pre-vaccination and post-vaccination periods for prevalence of HPV infections in four HPV types subgroups; first was high-oncogenic risk vaccine types (HPV16 and HPV18), second was three types with the greatest evidence of cross-protective efficacy (HPV31, HPV33, and HPV45), third was five potentially cross-protective types (HPV31, HPV33, HPV45, HPV52, and HPV58), and fourth was all high-oncogenic risk non-vaccine types (all high-risk HPV types except for HPV16 and HPV18) among girls age 13 to 19 years old and women age 20 to 24 years old, the results were stated in table 5. Other primary outcomes were frequency (prevalence or incidence) of anogenital wart diagnosis; and the frequency (prevalence or incidence) of high-grade cervical lesions.[18, level 1]

Table 5: HPV Infection Before HPV Vaccination (Pre-Vaccination) and After HPV Vaccination (Post-Vaccination).

HPV Sub-groups	Descriptions of HPV Sub-groups	Findings	
		Girls age from 13 to 19 years old	**Women age 20 to 24 years of age**
1	High-oncogenic risk vaccine types (HPV16 and 18)	Overall prevalence of HPV types 16 and 18 decreased significantly by 64% in the post-vaccination period (RR 0.36 [95% CI 0.25, 0.53]) compared with pre-vaccination period, with significant dose-response association with vaccination coverage (p = 0.005)	Overall prevalence for HPV types 16 and 18 was not significantly decreased (31%, RR 0.69 [95% CI 0.47, 1.01]) in the post-vaccination period. However, the dose-response association with vaccination coverage was significant (p = 0.01)
2	3 types with greatest evidence of cross-protective efficacy (HPV31, 33 and 45)	Overall prevalence significantly decreased by 28% (RR 0.72 [95% CI 0.54, 0.96] but the reduction was not associated with vaccination coverage	No significant decreases in prevalence or dose–response associations with vaccination coverage were recorded for HPV types 31, 33, and 45, or for

HPV Sub-groups	Descriptions of HPV Sub-groups	Findings	
		Girls age from 13 to 19 years old	**Women age 20 to 24 years of age**
3	5 potentially cross-protective types (HPV31, 33, 45, 52 and 58)	Overall prevalence of HPV types 31, 33, 45, 52, and 58, and non-vaccine high-risk types (i.e, all high-risk HPV types except HPV16 and HPV18) did not change significantly between the pre-vaccination and post-vaccination periods	HPV types 31, 33, 45, 52, and 58
4	All high-oncogenic risk non-vaccine types (all-high-risk HPV types except for HPV16 and 18)		Small but non-significant increase in non-vaccine high-risk HPV types occurred (RR 1·09, 95% CI 0·98–1·22), which was negatively associated with increasing vaccination coverage (p=0·03)

In countries that used quadrivalent HPV vaccine in their HPV vaccination programme, anogenital warts were significantly decreased by 31% (RR 0.69 [95% CI 0.60, 0.79]) in the post-vaccination period of girls at age of 15 to 19 years old. In the same population, the dose-response association was recorded between anogenital wart reduction and increased in population level female vaccination coverage (p = 0.0007). Besides that, the anogenital warts were reduced more substantially (by 61%) in studies with high vaccination coverage than in those with low vaccination coverage (14% reduction). In the population of women aged 20 to 39 years, there was non-significant decreased in anogenital warts were recorded at post-vaccination. The findings were similar in population of boys aged 15 to 19 years old, with 5% non-significant reductions of anogenital warts (RR 0.95 [95% CI 0.84, 1.08]). In countries with high female-vaccination coverage, the anogenital warts were significantly reduced by 32% in women aged 20 to 39 years (RR 0.68 [95% CI 0.51, 0.89]) and by 34% in boys aged 15 to 19 years old (RR 0.66 [95% CI 0.47, 0.91]). However, there was no changes in men aged 20 to 39 years in countries using the quadrivalent HPV vaccine.[18, level 1]

There was only one study which assessed population-level changes in anogenital warts following vaccination with bivalent vaccine. The study found that there was small but significant decreased in anogenital warts in girls aged of 15 to 19 years old. However, in contrary in boys aged 15 to 19 years old; there was significant small increment in the anogenital warts. For older people of either sex, there was no significant effect. There was also one study which recorded significant decreased in high-grade precancerous cervical lesions for girls aged 15 to 19 years old (RR 0.69, [95% CI 0.66, 0.73]) but no significant changed was recorded in two studies reporting data in women aged ≥20 years old.[18, level 1]

5.2.2 Immunogenicity and Non-Inferiority

Nonavalent HPV Vaccine

The SR by Signorelli C et al (2017) reported that two studies conducted immune-bridging efficacy studies which inferred nonavalent HPV efficacy in males and females aged nine to 15 years old, in heterosexual males and in men having sex with men (MSM) aged 16 to 26 years compared the immunogenicity data between individuals in the intervention arms and 16 to 26 years old female controls. Both studies reported at months seven, the GMTs in the intervention arms was non-inferior (lower bound of the two-sided 95% CI of the GMT ratio > 0.67) to the control arm from all nonavalent HPV vaccine types and the seroconversion non-inferiority in more than 99% of study

participants. For immunogenicity, all the included studies assessed the immunogenicity of nonavalent HPV vaccine. Three studies compared the immunogenicity of nonavalent HPV vaccine to quadrivalent HPV vaccine. The results of the studies showed that nonavalent HPV vaccine was non-inferior compared with quadrivalent HPV vaccine with regards to HPV types 6, 11, 16 and 18 in female and males aged 16 to 26 years. The GMT ratios range from 0.80 and 1.19 in the females and 0.89 to 1.23 in the males.[16, level 1]

There also two studies which reported on concomitant administration of nonavalent HPV with other vaccines (meningococcal [MCV4], tetanus, diphtheria, pertussis [Tdap] and polio vaccines). The studies found that there was non-inferior immune response and seroconversion rate for nonavalent HPV vaccine and the other vaccines in subjects receiving concomitant vaccine administration as compared with non-concomitant administration. Another study also showed that all nonavalent HPV types had seven months GMTs and SCRs non-inferiority in the concomitant group whereas the non-inferiority of immune response for diphtheria, tetanus, all pertussis and polio antigen were also established in both concomitant and non-concomitant group. The authors also reported that one study assessed the immunogenicity of nonavalent HPV vaccine versus placebo (normal saline) in females aged 12 to 26 years-old who were previously vaccinated with quadrivalent HPV vaccine. The seroconversion at month 7 was reported to be more than 98% for all nonavalent HPV types with marked elevations in GMTs. However, data from cross-study analysis showed that anti-HPV 31/33/45/52/58 GMTs to be lower than in study subjects administered nonavalent HPV vaccine who had not previously received quadrivalent HPV vaccine.[16, level 1]

For immunogenicity, Garland SM et al. reported that, in Study 001 (refer table 4), the GMTs for anti-HPV-6/11/16/18 at seven months were generally similar between quadrivalent HPV vaccine and nonavalent HPV vaccine groups within each country. Overall, ≥97.9% of participants were seroconverted within one month after the last nonavalent HPV vaccination to each of the vaccine types. Comparing between participants in Study 001 and Study 002 (refer table 4), the authors found that GMTs among young Indian women were similar or higher across HPV types compared with young women in the overall Study 001 population which indicated that HPV antibody responses in young Indian women were sufficient to induce high-level protective efficacy. Among Asian girls and boys in Study 002, GMTs for each of the nine HPV types were higher than in overall population of young women (N = 6,792) from Study 001 and the subgroups of young women from each corresponding country in Study 001. In term of SCRs, ≥98.8% of Asian girls and boys underwent SCRs at month seven to each of the nine HPV types. The results were similar when considering GMTs and SCRs for girls only.[17, level 1]

Petersen LK et al. (2017) summarized a combined analysis of five phase III clinical trials (Study 001, 002, 005, 007 and 009; refer table 4). The objective of the analysis was to examine antibody response in subgroups for which individual studies may have had limited sample size. The trials consisted of 11,304 subjects who were randomised to receive all three doses of nonavalent HPV vaccine or quadrivalent HPV vaccine and either HPV vaccine concomitant with or non-concomitant with other vaccine. Those five studies consisted of three main populations as showed in table 4. Serum samples of each participant were obtained at day 1 and month 7 for anti-HPV antibody testing. The serum samples were assessed for antibodies to HPV types 6/11/16/18/31/33/45/52/58. The outcome of the study was mainly on the SCRs. For all subjects, the SCRs at month

7 ranged from 99.6% to 100%. In study 002, GMTs at month seven were markedly higher in girls and boys than in women for all nonavalent HPV types and among the adolescent. The vaccine administration among boys resulted in marginally, higher anti-HPV GMTs than girls of the same age. The GMTs also decreased with increasing age. The authors also conducted subgroup analysis based on races and regions as shown in table 6 and table 7 respectively. By races, among women 16 to 26 years old; black women tended to have higher HPV GMTs than Asian or white women or women of another race. However, it was not consistent across all the nonavalent vaccine types. By regions, subjects in Africa, Latin America and North America tended to have higher anti HPV GMTs than subjects in Asia and Europe.[19, level 1]

Table 6: Sub-Group Analysis Based on Races

Per-protocol summary of anti-HPV geometric mean titers at month 7 by race in women 16–26 years of age who received 3 doses of 9vHPV vaccine.

	Race							
	Asian		Black		White		Other	
Assay	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	763	837.4 (793.1, 884.0)	123	935.3 (817.1, 1070.6)	2415	895.4 (868.5, 923.1)	1020	929.0 (886.5, 973.7)
HPV 11	764	594.5 (561.9, 629.0)	122	670.1 (581.8, 771.7)	2421	691.1 (669.5, 713.3)	1020	677.7 (645.4, 711.6)
HPV 16	792	3071.2 (2913.4, 3237.7)	132	3983.9 (3531.7, 4493.9)	2361	3077.8 (2985.2, 3173.4)	1056	3307.7 (3159.9, 3462.3)
HPV 18	831	850.9 (799.4, 906.7)	170	995.0 (866.8, 1142.3)	2669	755.6 (729.7, 782.3)	1214	886.2 (841.6, 933.2)
HPV 31	858	710.7 (667.6, 756.6)	169	786.4 (683.0, 905.5)	2631	619.5 (597.8, 642.1)	1148	725.1 (686.9, 765.4)
HPV 33	856	420.2 (397.1, 444.6)	189	414.6 (367.6, 467.5)	2733	417.1 (404.1, 430.5)	1278	424.0 (404.8, 444.0)
HPV 45	885	281.4 (262.9, 301.3)	190	345.0 (297.9, 399.6)	2824	227.3 (218.8, 236.1)	1261	290.1 (274.1, 307.2)
HPV 52	788	353.8 (332.7, 376.1)	166	444.0 (388.4, 507.5)	2690	388.2 (375.6, 401.4)	1148	381.0 (362.1, 400.8)
HPV 58	814	520.3 (490.5, 551.9)	161	493.1 (431.9, 562.9)	2720	483.6 (468.2, 499.4)	1123	480.8 (457.2, 505.5)

GMT, geometric mean titer (given in milli-Merck units per milliliter). CI, confidence interval.

Table 7: Sub-Group Analysis Based on Regions

Per-protocol summary of month 7 anti-HPV geometric mean titers by region in women 16–26 years of age who received 3 doses of 9vHPV vaccine.

	Region									
	Africa		Asia-Pacific		Europe		Latin America		North America	
Assay	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	16	1029.3 (708.5, 1496.1)	691	817.9 (772.7, 865.8)	1454	850.9 (818.2, 884.9)	1292	946.6 (908.1, 986.8)	868	953.2 (906.1, 1002.8)
HPV 11	15	764.4 (511.2, 1142.9)	692	588.9 (555.0, 624.8)	1458	660.0 (633.7, 687.5)	1292	686.0 (656.9, 716.4)	870	729.5 (692.0, 769.1)
HPV 16	20	5218.2 (3746.9, 7267.3)	722	2943.1 (2785.2, 3109.8)	1412	2929.3 (2816.1, 3047.1)	1336	3355.0 (3221.8, 3493.8)	871	3412.8 (3245.7, 3588.5)
HPV 18	21	1376.9 (930.3, 2037.7)	758	827.4 (775.1, 883.2)	1604	714.2 (682.9, 747.0)	1537	887.6 (847.9, 929.2)	964	838.4 (791.3, 888.3)
HPV 31	23	986.1 (673.5, 1443.9)	785	673.6 (631.0, 719.0)	1584	578.7 (552.7, 605.9)	1454	725.5 (691.6, 761.2)	960	717.3 (676.1, 760.9)
HPV 33	18	442.9 (300.3, 653.3)	782	407.1 (383.8, 431.9)	1635	396.9 (381.1, 413.4)	1616	429.3 (412.0, 447.3)	1005	450.9 (428.1, 475.0)
HPV 45	24	518.1 (343.1, 782.3)	810	267.7 (249.4, 287.4)	1714	207.8 (197.9, 218.2)	1604	291.0 (276.7, 306.1)	1008	272.0 (255.2, 289.8)
HPV 52	20	552.8 (376.5, 811.7)	717	340.6 (319.4, 363.2)	1620	365.1 (349.8, 381.0)	1465	390.8 (373.7, 408.8)	970	432.1 (409.0, 456.7)
HPV 58	15	706.9 (458.1, 1090.8)	743	497.3 (467.5, 528.9)	1647	468.2 (449.2, 487.9)	1425	482.8 (461.7, 504.7)	988	527.2 (499.8, 556.1)

GMT, geometric mean titer (given in milli-Merck units per milliliter). CI, confidence interval.

Analyses of month seven GMTs by race and by region in girls and boys nine to 15 years of age also provided similar results. The months seven GMTs were also markedly higher in girls and boys nine to 15 years of age than in women 16 to 26 years of age for all subgroups defined by race or region for all nine HPV types. The authors underwent exploratory analyses and observed an inverse relationship between mean HPV antibody responses at month seven and age regardless the race and region, even though all differences were observed among subgroups defined by race and region, no consistent pattern was demonstrated across all nine vaccine types. The GMTs were analysed over time in the per-protocol population and in subjects seropositive and PCR negative at day one in Study 001. The anti-HPV GMTs generated by nonavalent HPV vaccine were dramatically increased after two doses (month 3) or three doses (month 7) and were substantially higher than GMT's observed in the per-protocol population for all time points from month 3 to month 42.[19, level 1]

Iversen OE et al. (2016) conducted a RCT to determine whether HPV type-specific antibody responses would be non-inferior among girls and boys aged nine to 14 years after receiving two doses of the nonavalent HPV vaccine compared with adolescent girls and young women aged 16 to 26 years who received three doses. The intervention group was eligible girls and boys aged nine to 14 years who were healthy and not sexually active prior to enrolment (1,204 participants). Meanwhile, the control group was adolescent girls and young women aged 16 to 26 years (314 participants) who were healthy with ≤4 lifetime sexual partners and without history of abnormal Pap-Smear or other cervical abnormalities. In total, 1,518 participants enrolled in the trial. The primary end point was antibody response against HPV-6, -11, -16, -18, -31, -33, -45, -52 and -58 which was assessed just prior to the first dose of each assigned vaccine schedule. The secondary end point was SCRs prior to the first dose and one month after the last dose of given regimen. The follow-up was to assess antibody persistence through month 36. The antibody GMTs against the nonavalent HPV types assayed one month after the last dose were consistently higher in girls (vaccine dose at zero and six months) and boys (vaccine dose at zero and 12 months) than adolescent girls and young women (vaccine dose at zero, two and six months) in per-protocol population. The non-inferiority criteria of antibody GMTs were met for all nonavalent HPV types (all $p < 0.001$). For secondary outcome, 98% of participants in each cohort seroconverted by one month after the last vaccine dose to each individual HPV types of the vaccine. The authors found that the non-inferiority criteria for SCRs was met for all nonavalent HPV types (all $p<0.001$). The authors also conducted two post-hoc analysis to assess the persistence of antibody response at six months after the last dose in the vaccine groups who received two or three doses on six-month schedule. The antibody GMTs decline in all four cohorts over the five-months period. However, the ratio of antibody GMTs for responses after two doses in girls and boys relative to three doses in adolescent girls and young women were maintained above the noninferiority threshold. Second post-hoc analysis showed that in cohort of girls aged nine to 14 years receiving doses at zero, two and six months, the antibody GMTs against HPV types in the vaccine were higher in girls than in adolescent girls and young women aged 16 to 26 years old.[20, level 1]

Vaccination Programme (Quadrivalent and Bivalent HPV Vaccine)

Setiawan D et al. (2017) conducted a SR and MA to investigate the immunogenicity of HPV vaccines among both uninfected and infected populations in Asian countries (vaccination programme in Malaysia, Korea, Bangladesh, Japan, Hong Kong, India and China). The SR identified 10 studies which consisted of two quadrivalent vaccine studies and eight bivalent-vaccine studies conducted in Asian countries. Compared with

controls, there was higher number of seroconversions on HPV16- and HPV18-specific antibodies in the vaccinated groups compared with the controls and the difference was statistically significant; (RR 62.52; 95% CI 16.29,239.96 and RR 50.14; 95% CI 31.17,80.68 respectively). With respects to vaccine type, the pooled RR on SCR of HPV 16 for seven RCTs used the bivalent vaccine and two RCTs used quadrivalent vaccine was 44.86 (95% CI 11.90, 169.15) and 252.65 (95% CI 35.77, 1784.59), respectively. Meanwhile for RR and SCRs of HPV 18 with respects to the vaccine type; pooled studies of six trials used bivalent HPV vaccine showed the RR of 43.22 (95% CI 23.35, 73.68) and quadrivalent HPV vaccine, pooled RR of two studies showed that 96.04 (95% CI 33.87, 272.34). Further analysis of antibody levels in combination of both infected and uninfected individuals suggested that the HPV vaccines significantly enhanced the level of HPV16- and HPV18-specific antibody, RR 8.60 (95% CI 6.95, 10.64) and RR 8.13 (95% CI 5.96, 11.11), respectively. However, more data are needed to establish vaccine efficacy with regard to prevention of HPV infection and further outcomes including cervical intraepithelial neoplasia (CIN) and cervical cancer.[21, level 1]

5.2.3 Vaccination Coverage

Brisson M et al. (2016) conducted a SR and MA of model predictions of the long term population-level effectiveness of quadrivalent vaccine (HPV vaccination against HPV 6, 11, 16 and 18 infections) in women and men, to examine the robustness and variability of predicted herd effects, incremental benefit of vaccinating boys, and potential for HPV vaccine-type elimination. The authors identified 51 articles which were published by 19 different research teams. Out of 19 teams, 17 teams provided new standardized model predictions, however, only 16 models were included in the MA. The 16 models varied in terms of types (deterministic or stochastic), structures (assumptions about sexual activity, partnership formation and dissolution, transmission and natural immunity), and baseline HPV prevalence and were developed in ten countries (Australia, Canada, Finland, Germany, Ireland, Italy, Netherlands, Norway, United Kingdom and USA). The HPV 16, 18, 6 and 11 were included in 16, 13, five and three models, respectively. The authors independently identified HPV transmission-dynamic mathematical models from the published literature. Only univariate linear meta-regression was conducted. From the systematic search, 16 of 19 eligible models from 10 high-income countries provided predictions. The predictions were as follow:[22, level 1]

i. Base-case assumptions (Girls-only vaccination)
   a. 40% girls-only vaccination coverage
      - Relative reduction prevalence (RR_{prev}) of HPV 16 among women was 0·53 (80% uncertainty interval (UI) 0·46–0·68) and men was and 0·36 (UI 0·28–0·61), after 70 years

   b. 80% girls-only vaccination coverage
      - RR_{prev} of HPV 16 among women was 0·93 (UI 0·90–1·00) and men was 0·83 (UI 0·75–1·00), after 70 years

ii. Vaccinating boys in addition to girls
   a. 40% girls-only vaccination coverage
      - Increased the RR_{prev} of HPV 16 among women by 0·18 (UI 0·13–0·32) and men by and 0·35 (UI 0·27–0·39), after 70 years

b. 80% girls-only vaccination coverage
- Increased the RR_{prev} of HPV 16 among women was 0·07 (0·00–0·10) and among men was 0·16 (UI 0·01–0·25), after 70 years

For the same number of additional vaccinated individuals, increasing coverage in girls-only strategy was predicted to provide greater population-level benefits than was including boys in vaccination programme. The models predicted that increasing girls-only vaccination coverage by 40% (from 40% to 80%) reduced HPV 16, 18, 6 and 11 prevalence in women by an additional 40%, 38%, 35% and 19%, respectively; higher than the incremental benefits of vaccination 40% of boys in addition to 40% of girls. The same increase in girls-only vaccination coverage from 40% to 80% was also more effective in reducing HPV 16, 18 and 6 prevalence in men than the incremental benefit of vaccination 40% of boys in addition to 40% of girls and the strategies were equally effective for HPV 11. Increasing coverage considerably improved population level effectiveness up to 80% for girls-only vaccination and 60% for girl's and boy's vaccination, after which, increasing coverage had very little marginal benefit. Substantial herd effects were predicted with girls-only vaccination coverage as low as 20%. Based on the included models, 19% (three of 16 models), 46% (six of 13 models), 60% (three of five models) and 100% (three of three models) predicted that HPV 16, 18, 6 and 11, respectively, would be eliminated among heterosexual populations if girls-only vaccination reaches 80% coverage. The girl's and boy's strategy substantially increased the predicted potential for elimination; 64%, 92%, 80% and 100% of models predicted that HPV 16, 18, 6 and 11 would be eliminated with 80% coverage and few models predicted elimination of types HPV 18, 6 and 11 with 60% coverage. The authors conclude that elimination of HPV 16, 18, 6, and 11 was possible if 80% coverage in girls and boys reached and if high vaccine efficacy was maintained over time.[22, level 1]

5.3 SAFETY

The United State Food and Drug Administration (USFDA) approved the nonavalent HPV vaccine on December 10, 2014 for use in females aged 9 to 26 years and males aged nine to 15 years.[8,23] The European Union (EU) and Australia approved the nonavalent HPV vaccine in June 2015. In EU the age was up to 45 years old.[9]

Costa APF et al. (2017) conducted an analysis to assess whether the nonavalent HPV vaccine was safe as quadrivalent vaccine in the female population. After systematic search, the authors included three RCTs which involved a total of 27,465 participants. From the analysis, they found that both nonavalent and quadrivalent HPV vaccines had similar systemic adverse events (AEs); headache, dizziness and fatigue. However, more fever, pruritus, gastrointestinal (GI) symptoms and injection-site related (local AEs) in the nonavalent HPV vaccine compared to quadrivalent. The detailed of the adverse events are shown in table 8. The authors also found serious vaccine-related AEs in both HPV vaccines; out of more than 27,465 vaccinated participants, a total of 29 (0.11%) participants in nonavalent HPV vaccine group and 23 (0.084%) participants in quadrivalent HPV vaccine group experienced serious vaccine-related AEs. However, the authors did not describe in detail of the serious vaccine-related AEs. There was also a total of six deaths recorded from each group but none was judged to be vaccine related.[24, level 1]

Table 8: Adverse Events of Nonavalent HPV Vaccine versus Quadrivalent HPV Vaccine

Adverse Events	Nonavalent HPV Vaccine (Total Events [%])	Quadrivalent Vaccine (Total Events [%])	Odd Ratios; CI
Headache	1,662 (5.75%)	1,573 (5.44%)	OR 1.07; 95% CI 0.99–1.15
Dizziness	334 (1.156%)	308 (1.07%)	OR 1.09; 95% CI 0.93–1.27
Fatigue	265 (0.92%)	244 (0.84%)	OR 1.09; 95% CI 0.91–1.30
Fever	462 (1.60%)	393 (1.36%)	OR 1.18; 95% CI 1.03–1.36
Pruritus	538 (1.86%)	379 (1.31%)	OR 1.44; 95% CI 1.26–1.15
GI Symptoms	538 (1.86%)	412 (1.43%)	OR 1.24; 95% CI 1.09–1.45
Pain	11,837 (40.34%)	10,492 (35.58%)	OR 1.72; 95% CI 1.62–1.82
Erythema	3,279 (11.12%)	2,727 (9.25%)	OR 1.29; 95% CI 1.21–1.36

Moreira ED et al. (2016) conducted an analysis of seven Phase III clinical trials to summarise the overall safety profile of the nonavalent HPV. The study involved males and females (non-pregnant at entry) at age nine to 26 years old. The description of the studies is summarised in table 9. Both HPV vaccines (nonavalent and quadrivalent HPV vaccine) was administered as a three doses regimen at day one, months two and months six. More than 15,000 subjects received one or more dose of nonavalent HPV vaccine. In two studies, more than 7,000 control subjects received one or more dose of quadrivalent HPV vaccine. The most common AEs (≥5%) experienced by nonavalent HPV vaccine recipients were injection-site AEs (pain, swelling, and erythema) and vaccine-related systemic AEs (headache, and pyrexia). Injection-site AEs were more common in nonavalent HPV vaccine than quadrivalent HPV vaccine recipients at mild-to-moderate in intensity. Discontinuations and vaccine-related serious AEs were rare (0.1% and <0.1%, respectively). Seven deaths were reported; none were considered vaccine related.[25, level 1]

Table 9: Phase III Studies of Nonavalent HPV Vaccine Contributing to the Combined Safety Analysis

Phase III Studies	Population involved				Study Description
	Girls (ages; total number)	Boys (ages; total number)	Women (ages; total number)	Men (ages; total number)	
Study 001 (NCT00543543)	-	-	Age: 16 – 26yr N = 14,185	-	Subjects were randomised to receive 9vHPV or 4vHPV vaccines
Study 002 (NCT00943722)	Age: 9 – 15 yrs n = 1,933	Age: 9–15 yrs n = 666	Age: 16-26 yr n = 467	-	All participants receive 9vHPV vaccine
Study 003 (NCT01651949)	-	-	Age: 16-26 yr n = 1,099	Age: 16-26yr n = 1,416	All participants received 9vHPV vaccine
Study 005 (NCT00988884)	Age 11-15 yr n = 620	Age 11-15 yr n = 617	-	-	All participants received 9vHPV vaccine
Study 006 (NCT01047345)	Age 12-15 yr n = 120	Age 16-26 yr n = 493	-	-	Subjects were randomized to receive 9vHPV vaccine or saline placebo
Study 007 (NCT01073293)	Age 11-15yr n = 526	Age 11-15yr n = 526	-	-	all participants received 9vHPV vaccine
Study 009 (NCT01304498)	Age 9-15 yrs N = 598	-	-	-	Subjects were randomized to receive 9vHPV or 4vHPV vaccines

*9vHPV = Nonavalent HPV Vaccine
*4vHPV = Quadrivalent HPV Vaccine

Garland SM et al. also evaluated the safety of nonavalent HPV vaccine over quadrivalent vaccine. The authors recorded the oral temperature for five days and the injection-site reaction and the systemic AEs were recorded for 15 days. The authors pre-specified serious adverse events (SAEs) as those considered life threatening by investigator or resulted in death, significant disability or incapacity or prolong existing hospitalisation or were a congenital anomaly or cancer or another important medical event. Overall, the incidences of AEs, SAEs and new medical conditions were generally similar in both younger (nine to 15 years old) and older (16 to 26 years old) female patients. In study 001 which compared the vaccination effects on young women, injection-site AEs in five Asia countries (Hong Kong/Taiwan, South Korea, Japan and Thailand) were more common among nonavalent HPV vaccine group compared to quadrivalent vaccine group. The injection-sites AEs reported were pain, swelling and erythema which was described as mild to moderate intensity. For systemic AEs, the pproportions of participants from Hong Kong/Taiwan, Japan, and South Korea who experienced a vaccine-related systemic AE (nonavalent HPV vaccine, 11.8%–18.8%; quadrivalent HPV vaccine, 6.3%–13.9%) were lower than in the overall study population (nonavalent HPV vaccine, 29.5%; quadrivalent HPV vaccine, 27.3 %). In the Study 002 which compared girls and boys, the most common injection-site AEs were also pain, swelling and erythema which were mostly mild to moderate intensity. In both studies, no SAEs were reported for the entire study duration. There were three deaths among Asian participants in Study 001 but none of the death were considered as HPV vaccine related.[17]

Signorelli C et al. reported the safety findings in their SR based on nine included trials. In study that compared nonavalent HPV vaccine with quadrivalent vaccine, the AEs events (injection-site events, systemic events, and serious adverse events) were more in nonavalent HPV vaccine than in quadrivalent vaccine. The study also showed that AEs among females were higher compared to male. The authors also assessed the AEs in concomitant vaccines administration between nonavalent HPV vaccine and other vaccines in two difference studies. First study compared concomitant group (nonavalent HPV vaccine with MCV4 and Tdap at different arms) with non-concomitant group (nonavalent HPV vaccine at day 1 and MCV4 and Tdap one month after at different arm). The study showed that swelling at nonavalent HPV vaccine injection site in concomitant group was significantly higher than non-concomitant group; 14.4% versus 9.4%, respectively. Second study compared concomitant group (nonavalent HPV vaccine with Tdap-IPV at different arms) with non-concomitant group (nonavalent HPV vaccine at day 1 and Tdap-IPV one month after at different arm. The study also showed that swelling at nonavalent HPV vaccine injection site was significantly higher in concomitant than non-concomitant group; 13.0% and 8.2%, respectively. In placebo-controlled trial where the females involved were previously vaccinated with quadrivalent vaccine, injection-site AEs were more frequent in nonavalent HPV vaccine 91.1% compared to placebo armed (43.9%). The incidence was increased with subsequent nonavalent HPV vaccine dose.[16]

Iversen OE et al. (2016) found that 22 (1.45%) out of 1,518 participants experienced SAEs. However, they were not related to the vaccine. There was one participant (9-years old girl) who discontinued the study because of vaccine-related ADR; transient urticarial one day after the first dose which fully resolved. No death was reported during the study.[20]

Setiawan D et al. reported that HPV vaccination among Asian populations has a favourable safety profile, with only slightly higher risks of local (RR: 1.89; 95% CI 1.65, 2.17) and systemic (RR: 1.33; 95% CI 1.18,1.50) adverse events in vaccinated individuals compared with controls.[21]

5.4 COST/COST-EFFECTIVENESS

Ng SS. (2018) conducted SR of cost-effectiveness to update the economic evidence on HPV vaccination, by focusing on (i) Nonavalent vaccine compared to bivalent or quadrivalent vaccine; (ii) Gender-neutral vaccination compared to female only vaccination; and (iii) Multiple age cohort immunisation compared to single age cohort immunisation. Thirty-four studies were included in the review and 28 of them were conducted in high income countries (USA, UK, Netherlands, Italy, Taiwan, Austria, Canada, Denmark, Norway, and Hungary). The SR reported that in:[26]

i. Nonavalent vaccine compared to bivalent or quadrivalent vaccine
- Inconclusive evidence to proof greater cost-effectiveness of nonavalent vaccine compared to the older HPV vaccines as the price of nonavalent vaccine was still uncertain

ii. Gender-neutral vaccination compared to female only vaccination
- Inclusion of adolescent boys in vaccination programme was found to be cost-effective if the vaccine price and the coverage was low
- However, when coverage for female was above 75%, gender neutral vaccination was less cost-effective than when targeting only girls aged nine–18 years

iii. Multiple age cohort immunisation compared to single age cohort immunisation
- Multi cohort immunisation strategy was cost-effective in the age range nine–14 years but the upper age limit at which vaccination were no longer cost-effective needs further assessment

The key influential parameters identified were duration of vaccine protection, vaccine price, vaccine coverage, and discounting rates. The HPV protection in women has been shown to last for at least 9.4 years with bivalent vaccine and at least 10 years with quadrivalent vaccine, with a trend of sustained protection up to 12 years of follow-up. Most of the studies varied the duration of protection between 10 and 20 years in their sensitivity analysis. The vaccine price plays an important role in order to determine the cost-effectiveness of the vaccination programme. In Brazil, when the vaccine price increased from US$12 to US$135 per dose, vaccinating adolescent boys in addition to girls was no longer cost-effective even when vaccine coverage for female was minimised to 25%. In one study, the ICER may fall below the lower range of CEA threshold (≤ €20,000/QALY) when vaccine price was reduced by 38% and multicohort strategy became very cost-effective. When the vaccine coverage for female was above 70% to 80%, the benefits of gender-neutral vaccination became rather small as the additional health gains for female were almost negligible, while the cost nearly doubled. The included studies found that the evaluation of future health outcomes for HPV vaccination was highly dependent on the discounting adopted. One study stated that undiscounted and discounted net present value of gender-neutral HPV vaccination. The study showed that the ICER increased when the discount rate increased and vaccinating both genders was not cost-effective at higher discount rate of 5%. In contrast the gender-neutral vaccination became more cost-effective in undiscounted analysis.[26]

Mennini FS et al. (2017) conducted a cost-effectiveness study to provide realistic estimates of the epidemiological and economic impact of the implementation of the nonavalent HPV vaccine programme for both girls and boys in Italy compared to the current clinical practice using a quadrivalent HPV vaccine (HPV 6/11/16/18) or bivalent HPV vaccine (HPV 16/18) for girls only. The time horizon of the study was short and long-term at the perspective of national health service. The authors generated a deterministic model which was used to estimate the total number of disease events associated with related HPV vaccine types (6/11/16/18/31/45/52/58), the incidence and mortality (cervical cancer, CIN, anal cancer and genital warts); the costs of vaccination, screening, diagnosis and management of the disease; the quality adjusted life years (QALYs) of the model population. Results were reported over 100 years for the different strategies tested. The results of the analysis were divided into epidemiology and cost-effectiveness as follow:[27]

i. Epidemiological Results

The nonavalent HPV vaccine girls-only vaccination and the quadrivalent HPV vaccine girls-only vaccination was associated with a 76% and 63% decrease in incidence of cervical cancer respectively, over 100 years. Overall, the estimated number of cervical disease events prevented with the nonavalent HPV vaccine in 100 years in comparison with the quadrivalent HPV vaccine was 16,678 for cervical cancer, 82,598 for CIN1, and 127,742 for CIN2+. In total, the reduction in the number of cases of pre-cancerous lesions (CIN 1, CIN 2/3) and genital warts occurred within 5th years of the start of the vaccination programme. The reduction in incidence of HPV-related cancers and deaths from HPV-related cancers was more gradual, reflecting the fact that HPV related cancers were diseases with slower progression. Switching from a girl-only vaccination with the quadrivalent HPV vaccine to a universal vaccination with the nonavalent HPV vaccine showed significant health benefits. With respect to the quadrivalent HPV vaccine, additional 22,640 prevented cases of cervical cancer, 105,431 of CIN1, and 170,286 of CIN2+ were associated with the nonavalent HPV vaccine universal vaccination. Furthermore, the comparison between the nonavalent HPV vaccine universal vaccination and the quadrivalent HPV vaccine girls-only vaccination estimated that vaccinating boys will prevent 1,508,505 cases of genital warts among males, 358,140 cases of genital warts among females, and 8,111 cases of anal cancer. The details of the estimated comparison were showed in table 10.

Table 10: Disease Events Prevented with the Nonavalent HPV Vaccine Universal Vaccination in Comparison with the Current Strategy (the Quadrivalent Vaccine Girls-Only Vaccination)

Disease event	Years since start of vaccination programme			
	5	25	50	100
Females				
Cervical cancer	0	367	4623	22,640
CIN 1	23	6961	34,753	105,431
CIN 2/3	25	10,193	54,709	170,286
Vaginal cancer	0	0	13	88
VAIN 2/3	0	0	0	0
Vulvar cancer	0	1	21	130
Genital warts and HPV 6/11-related CIN 1	33	2438	6270	13,658
Genital warts	1411	61,285	161,443	358,140
Anal cancer	0	11	318	2619
Males				
Genital warts	6101	208,935	615,645	1508,705
Anal cancer	0	28	748	5492

ii. Cost-Effectiveness

The ICER for nonavalent HPV vaccine compared with quadrivalent HPV vaccine was 4,483€/QALY when considering girls-only vaccination and 10,463€/QALY for a nonavalent HPV vaccine universal vaccination. The implementation of the nonavalent HPV universal vaccination in comparison to a girls-only programme with the quadrivalent HPV vaccine was associated with a cost per QALY gained of €13,541. Details of the analysis was in table 11. In the instance where the vaccination covered only girls, the nonavalent HPV vaccine was cost-saving in comparison to the bivalent HPV vaccine.

Table 11: Cost-Effectiveness Results of the Base Case Analysis

Comparison		New technology		Comparator		Incremental costs	Incremental QALYs	Cost per QALY gained
New tech	Comparator	Costs	QALYs	Costs	QALYs			
HPV9 girls	HPV4 girls	€183.29	27.53857	€180.60	27.53797	2.69	0.0006	€4483
HPV9 girls	HPV2 girls	€183.29	27.53857	€188.92	27.53571	−5.63	0.00286	*Cost saving*
HPV9 universal	HPV4 universal	€213.64	27.54041	€206.63	27.53974	7.01	0.00067	€10,463
HPV9 universal	HPV4 girls	€213.64	27.54041	€180.60	27.53797	33.04	0.00244	€13,541

Meanwhile, comparison of the nonavalent HPV vaccine with the screening-only strategy showed an ICER of 2,592€/QALY for the girls-only vaccination and 5,855€/QALY in the case of a universal vaccination. The authors also conducted price threshold analysis, and the analysis showed that switching from the quadrivalent HPV vaccine to the nonavalent HPV vaccine girls-only vaccination was cost-effective up to a price of €201 per dose, considering a threshold for the ICER of €40,000/ QALY.

The authors also conducted sensitivity analysis. The analysis showed that bivalent vaccine remained dominated by the nonavalent HPV vaccine in all the sensitivity analysis. Overall, the ICERs were very sensitive to the discount rate.[27]

Local economic evaluation has been conducted by Woo YL et al. to assess the public health impact and cost-effectiveness of vaccination with nonavalent HPV vaccine programme for adolescent females in Malaysia. The analysis was funded by pharmaceutical company. Full assessment of the study could not be done as it is still unpublished and only the abstract was available. Based on the abstract, the nonavalent HPV vaccine resulted in fewer cases of CIN2/3 and cervical cancer compared with quadrivalent HPV vaccine and bivalent HPV vaccine. The authors also found that the incidence of CIN1 cases and genital warts was lesser in nonavalent HPV vaccine group than quadrivalent HPV vaccine and bivalent HPV vaccine, respectively. The study reported that disease management costs in nonavalent HPV vaccination was reduced compared with quadrivalent HPV vaccination and bivalent HPV vaccination; RM89,580,555 and RM1,201,631,851, respectively. The ICER of vaccination with 9-valent HPV compared to vaccination with 4-valent HPV and vaccination with 2-valent HPV was RM25,777/QALY- gained and RM13,038/QALY-gained respectively.[28]

Financial Implication of National HPV-Vaccination Programme

Financial implication of using nonavalent HPV vaccine in national HPV-vaccination programme was conducted. With a total of 230,000 school-girl vaccinated per year, the difference from the current national HPV-vaccination programme to nonavalent HPV-vaccination programme is expected approximately >90% increase in expenditure.

5.5 LIMITATIONS

Although there was no restriction in language during the search, but only English full text articles were included in this report. Only one reviewer involved in the study selection and appraisal. Although there was a local cost-effectiveness study conducted, but there was no full text article retrieved.

6. CONCLUSION

Efficacy / Effectiveness

iv. Infections Risks

Among non-HPV infected populations (female aged 16 to 26 years old), nonavalent HPV vaccine was highly effective in reducing diseases related to HPV types that were covered by the nonavalent HPV vaccine. Compared with quadrivalent HPV vaccine, there was no cases of cervical disease, vulva disease or vaginal disease related to HPV 31, 33, 45, 52 and 58 were detected in nonavalent HPV vaccinated group. Furthermore, HPV-52 and 58 related infections were most frequent in all countries with quadrivalent HPV vaccination.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the overall prevalence of HPV types 16 and 18 in girls aged 13 to 19 years old was significantly decreased compared with in women aged 20 to 24 years old. However, for HPV types 31, 33, 45, 52 and 58 and non-high-oncogenic risk, the overall prevalence

was not significantly changed. In high-female vaccination coverage, anogenital warts was significantly reduced in girls and boys aged 15 to 19 years old, and women 20 to 35 years old women.

v. Immunogenicity and Non-Inferiority

Within one to seven month, the nonavalent HPV vaccine successfully seroconverted with high GMTs level for all the HPV types covered. Compared with quadrivalent vaccine, the immunogenicity and non-inferiority response was similar for HPV 16, 18, 6 and 11. In terms of age, the GMTs level decreased as the age increased; the GMTs level for all HPV types covered by nonavalent HPV vaccine was higher in girls and boys aged nine to 15 years old than in women aged 16 to 26 years old. Among Asian populations, Indian females showed highest GMTs level than other races.

Concomitant administration of nonavalent HPV vaccine with MCV4 vaccine, Tdap vaccine and polio vaccine showed positive results as non-concomitant group. The nonavalent HPV vaccine was successfully seroconverted with elevated GMTs for all HPV types covered by the vaccine. Meanwhile, the immune response for other vaccine; diphtheria, tetanus, all pertussis and polio antigen were also established.

Girls and boys aged nine to 14 years old receiving the two doses of nonavalent HPV vaccine was non-inferior to a three doses nonavalent HPV vaccine in adolescent girls and young women aged 16 to 26 years old.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the seroconversion was significantly higher for both HPV types 16 and 18.

vi. Vaccination Coverage

Strong herd effects were expected from vaccinating girls-only at 40% coverage or even with coverage as low as 20%. Besides that, with high female-vaccination coverage (70% to 80%), the anogenital warts were significantly reduced by 32% in women (age of 20 to 39 years old) and boys (age of 15 to 19 years old). On the other hand, additional boys in girls-only vaccination just resulted in small increment in relative reduction prevalence (RR_{prev}) in both women and men.

Overall, the prevalence of HPV types 16 and 18 were significantly reduced in girls aged 13 to 19 years old and not significantly reduced in women aged 20 to 24 years old. However, the association of dose response and vaccination coverage was significant in the women group compared to the girl's group. Although, the prevalence of HPV types 31, 33, 45, 52 and 58 was significantly reduced in girls (aged 13 to 19 years old), no significant association between dose response and vaccination coverage were observed.

Safety

Based on above review, the adverse events were more common in nonavalent HPV vaccine compared to quadrivalent HPV vaccine. The most common AEs were fever, pruritus, GI symptom and injection-site related AEs. There was also small number of serious AEs reported which more cases were occurred in nonavalent HPV vaccine than quadrivalent vaccine. However, the SAEs was not described in detail. There were no death-related to the HPV vaccine reported.

By gender, more adverse events occurred among females than male's population. The adverse events were also more common in concomitant vaccination compared to non-concomitant vaccination.

Cost / Cost-Effectiveness

The SR of cost-effectiveness which included studies published within 2013 to 2016, concluded that if the HPV vaccination coverage for female was above 75%, gender neutral vaccination was less cost-effective than when targeting only girls aged nine to 18 years. However, the multi cohort immunisation strategy was cost-effective in the age range nine to 14 years but the upper age limit which vaccination were no longer cost-effective needs further assessment. There was inconclusive evidence to proof greater cost-effectiveness of nonavalent HPV vaccine compared to the quadrivalent or bivalent HPV vaccine as the price for nonavalent HPV vaccine was still uncertain.

One cost-effectiveness study conducted in Italy showed that switching from the quadrivalent HPV vaccine to the nonavalent HPV vaccine girls-only vaccination was cost-effective. Although there was a local cost-effectiveness study conducted, however, no full-text article was retrieved. Financial implication of using nonavalent HPV vaccine in national HPV-vaccination programme was conducted. The difference from the current national HPV-vaccination programme to nonavalent HPV-vaccination programme is expected approximately >90% increase in expenditure. Overall, the cost-effectiveness of nonavalent HPV vaccine in Malaysia was inconclusive with potentially high budget implication.

8. REFERENCES

1. Bray F, Ferlay J, Soerjomataram I et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Ca Cancer J Clin. 2018; 0:1–31
2. Manini I & Montomoli E. Epidemiology and Prevention of Human Papillomavirus. Ann Ig. 2018; 30 (1): 28-32
3. Khoo SP, Bhoo-Pathy N, Yap SH et al. Prevalence and Sociodemographic Correlates of Cervicovaginal Human Papillomavirus (HPV) Carriage in Cross-Sectional, Multi-ethnic, Community-Based Female Asian Population. Sex Transm Infect. 2017; 1-7
4. Tan SC, Ismail MP, Duski DR et al. Prevalence and Type of Distribution of Human Papillomavirus (HPV) in Malaysian Women with and Without Cervical Cancer: An Update Estimated. Bioscience Reports. 2018; 38
5. HPV and Cervical Cancer. WHO. 24 Jan 2019 Available at https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer Accessed on 29/7/2019
6. Schuchat A. What We Talk About When We Talk About HPV Coverage. N Engl J Med. 2015; 372 (8): 775-776
7. Maharita MR. Cervical Cancer Vaccine: Gardasil® and Cervarix®. Ministry of Health, Putrajaya, Malaysia. Technology Review Report. 008/2011. MaHTAS
8. Haghshenas MR, Mousavi T, Kheradmand M et al. Efficacy of Human Papillomavirus L1 Protein Vaccnes (Cervarix and Gardasil) in Reducing the Risk of Cervical Intraepithelial Neoplasia: A Meta-analysis. Int J Prev Med. 2017; 8:44
9. Zhang Z, Zhang J, Xia N et al. Expanded Strain Coverage for a Highly Successful Public Health Tool: Prophylactic 9-Valent Human Papillomavirus Vaccine. Hum Vaccin Immunother. 2017 Oct 3;13(10):2280-2291. doi: 10.1080/21645515.2017.1346755
10. Lapalco PL, Spotlight on the 9-Vaent HPV Vaccine. Drug Design, Development and Therapy. 2017; 11:35-44
11. Kavanagh K, Pollock KG, Cuschieri K et al. Changes in the Prevalence of Human Papillomavirus Following a National Bivalent Human Papillomavirus Vaccination Programme in Scotland: a 7-yeaar Cross-sectional Study. Lancet Infect Dis. 2017; 17: 1293-1302
12. Comprehensive Cervical Cancer Control. A Guide to Essential Practice. Chapter 4. 2nd Edition. WHO Available at https://www.who.nt/reproductivehealth/publications/cancers/cervical-cancer-guide/en Accessed on 29/7/2019
13. The Immunological Basis for Immunization Series. World Health Organisation. Available at: https://www.who.int/immunization/hpv/learn/immunological_basis_for_immunization_module19_who_2011.pdf Accessed on: 18 Jun 2019
14. Nor Asiah M, Saidatul Norbaya B, Safurah J et al. Achieving High Uptake of Human Papillomavirus Vaccination in Malaysia through School-Based Vaccination Programme. BMC Public Health. 2018; 18: 1402
15. Saidatul Norbaya B. et al. Human Papillomavirus Immunisation of Adolescent Girls: Improving Coverage through Multisectoral Collaboration in Malaysia. BMJ. 2018; 363: k4602
16. Signorelli C, Odone A, Ciorba V et al. Human Papillomavirus 9-Valent Vaccine for Cancer Prevention: a Systematic Review of the Available Evidence. Epidemiol. Infect. 2017; 145:1962-1982

17. Garland SM, Pitisuttithum O, Cho CH et al. Efficacy, Immunogenicity and Safety of a 9-Valent Human Papillomavirus Vaccine: Subgroup Analysis of Participants from Asian Countries. JJD. 2018; 218:95-108
18. Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Baeur H et al. Population-Level Impact and Herd Effects Following Human Papillomavirus Vaccination Programmes: Systematic Review and Meta-Analyses. Lancet Infect Dis. 2015; 15(5): 565-580
19. Peterson LK, Restrepo J, Moreira Jr et al. Impact of Baseline Covariates on the Immunogenicity of the 9-valent HPV Vaccine- A Combined Analysis of Five Phase III Clinical Trials. Papillomavirus Res. 2017; 3:105-115.
20. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E et al. Immunogenicity of the 9-Valent HPV Vaccine using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. JAMA. 2016; 316(22):2411-2421
21. Setiawan D, Luttjeboer J, Pouwels KB et al. Immunogenicity and Safety of Human Papillomavirus (HPV) Vaccination in Asian Populations from Six Countries: A Meta-Analysis. Japan J of Clin Oncol. 2017; 47(3): 265-276
22. Brisson M, Benard E, Drolet M et al. Population-Level Impact, Herd Immunity, and Elimination After Human Papillomavirus Vaccination: A Systematic Review and Meta-analysis of Predictions from Transmission-dynamic Models. Lancet Public Health. 2016;1: e8-17
23. Petrosky E, Bocchini JA, Hariri S et al. Use of 9-valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR. 2015; 64 (11)
24. Costa APF, Cobucci RNO, de Silva J et al. Safety of Human Papillomavirus 9-valen Vaccine: A Meta-Analysis of Randomized Trials. J Immunol Res. 2017; 2017:3736201
25. Moreira ED, Block SL, Ferris D et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Paediatrics. 2016; 138
26. Ng SS, Hutubessy R, & Chaiyakunapruk N. Systematic Review of Cost-Effectiveness Studies of Human Papillomavirus (HPV) Vaccination: 9-Valent Vaccine, Gender-Neutral and Multiple Age Cohort Vaccination. Vaccine. 2018; 36(19): 2529-2544
27. Mennini FS, Bonanni P, Bianic F et al. Cost-Effectiveness Analysis of the Nine-Valent HPV Vaccine in Italy. Cost Eff Resour Alloc. 2017; 15:1
28. Woo YL, Hsu TY, Pavelyev A et al. The Public Health Impact and Cost-effectiveness of School-based Nine-valent Human Papillomavirus Female Vaccination Compared with Bivalent and Quadrivalent Vaccination in Malaysia (ABSTRACT)
29. Huh WK. Joura EA, Giuliano AR et al. Final Efficacy, Immunogenicity and Safety Analyses of a Nine-Valent Human Papillomavirus Vaccine in Women Aged 16-26 Years: A Randomised, Double-Blind Trial. Lancet. 2017; 390 (10108): 2143 – 2159

9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to January 07, 2019

1 Papillomavirus infection.mp. or Papillomavirus Infections/ (23932)
2 Human papillomavirus$.tw. (31813)
3 (Hpv adj1 infection*).tw. (10876)
4 (Human adj1 papillomavirus$ infection*).tw. (3166)
5 Papillomavirus$ infection*.tw. (3738)
6 Papillomaviridae/ or Papillomavirus Infections/ or Human papillomavirus.mp. (45141)
7 1 or 2 or 3 or 4 or 5 or 6 (46300)
8 Cervical cancer.mp. or Uterine Cervical Neoplasms/ (82331)
9 (Cancer* adj1 cervi$).tw. (42539)
10 (Cancer* adj1 uterine cervi$).tw. (1777)
11 (Uterine adj1 cervi$ cancer*).tw. (1771)
12 Uterine cervi$ neoplasm*.tw. (56)
13 (cervi$ neoplasm* adj1 uterine).tw. (56)
14 Cancer* of cervi$.tw. (2252)
15 Cancer* of the cervi$.tw. (6424)
16 Cancer* of the uterine cervi$.tw. (1917)
17 (Cervi$ adj1 neoplasm*).tw. (459)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (84771)
19 PAPILLOMAVIRIDAE.mp. or PAPILLOMAVIRIDAE/ (23203)
20 Papillomaviridae.tw. (94)
21 HPV, human papillomavirus virus$.tw. (0)
22 (Virus$ adj1 human papilloma).tw. (5413)
23 (Virus$ adj1 human papillomavirus$).tw. (163)
24 (Human adj1 papilloma virus$).tw. (5415)
25 (Human adj1 papillomavirus$ virus$).tw. (77)
26 19 or 20 or 21 or 22 or 23 or 24 or 25 (26598)
27 CERVICAL INTRAEPITHELIAL NEOPLASIA.mp. or Cervical Intraepithelial Neoplasia/ (12347)
28 (Cervi$ adj1 intraepithelial neopla$).tw. (7519)
29 (Neoplas$ adj1 cervi$ intraepithelial).tw. (7514)
30 Cervi$ intraepithelial neoplas$ grade iii.tw. (107)
31 27 or 28 or 29 or 30 (12498)
32 7 or 18 or 26 or 31 (113558)
33 Gardasil-9.mp. (29)
34 Gardasil-9.tw. (27)
35 PAPILLOMAVIRUS VACCINES.mp. or Papillomavirus Vaccines/ (6787)
36 Hpv vaccine$.tw. (4452)
37 Human papilloma virus$ vaccine$.tw. (126)
38 (Vaccine$ adj1 human papillomavirus$).tw. (1215)
39 (Human adj1 papillomavirus$ vaccine*).tw. (1206)
40 (Papillomavirus$ adj1 vaccine*).tw. (1255)
41 Nonavalent hpv vaccine$.tw. (0)

42 Nano valent hpv vaccine$.tw. (0)
43 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (8293)
44 Papillomavirus Vaccines/ or Cervarix.mp. (6728)
45 Papillomavirus Vaccines/ or Bivalent vaccine.mp. (7057)
46 Cervarix.tw. (235)
47 Bivalent vaccine*.tw. (550)
48 35 or 36 or 37 or 38 or 39 or 40 or 44 or 45 or 46 or 47 (8728)
49 Papillomavirus Vaccines/ or quadrivalent vaccine.mp. (6863)
50 Gardasil.mp. or Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18/ (863)
51 Human papillomavirus$ recombinant vaccine* quadrivalent types 6, 11 ,16 18.tw. (0)
52 Gardasil.tw. (405)
53 human papillomavirus vaccine l1, type 6,11,16,18.tw. (0)
54 hpv l1 vaccine, quadrivalent 6,11,16,18.tw. (0)
55 35 or 36 or 37 or 38 or 39 or 40 or 49 or 50 or 51 or 52 or 53 or 54 (8483)
56 32 and 43 (7866)
57 32 and 43 and 48 (7861)
58 32 and 43 and 55 (7866)
59 32 and 43 and 48 and 55 (7861)
60 limit 59 to meta analysis (58)
61 limit 59 to randomized controlled trial (274)
62 limit 59 to systematic reviews (349)
63 limit 56 to meta analysis (58)
64 from 62 keep 1-2,4-5,9,11-15,17-18,23-24,27-29,32-33,35,37-39 (23)
65 from 34 keep 12,14,18,20-21 (5)
66 limit 47 to systematic reviews (15)
67 limit 52 to systematic reviews (12)
68 43 and 48 and 55 (8287)
69 from 60 keep 5-11,14,16,24-30,32-34,36,38-39,46-48,50,52,56 (28)
70 from 66 keep 1-2,4,6,9 (5)

OTHER DATABASES	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	Gardasil 9, Nonavalent HPV vaccine, 9vHPV
NHS economic evaluation database	
INAHTA	
FDA	
Others (Google Scholar, Google)	

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)