TECHNOLOGY REVIEW (MINI-HTA)

HPV VACCINE – AN UPDATE

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

The HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are considered as high-risk HPV genotypes. On top of that, the HPV16 and HPV18 are the most common genotypes in women worldwide and are associated with most cases of invasive cervical cancer. As prevention, three prophylactic HPV vaccines are available; bivalent HPV vaccine (2vHPV vaccine), quadrivalent HPV vaccine (4vHPV vaccine) and nonavalent HPV vaccine (9vHPV vaccine).

Previously in 2007, the World Health Organisation (WHO) recommended three-dose schedule of HPV vaccination for young girls. Later on, in new guideline update and based on available evidence at that time, WHO approved two-dose schedule for young girls age nine to 13 years old. On top of that, there were studies reported that the structural characteristics of the virus-like particles of the vaccine allowed an efficient production of the long-lived plasma cells, which continuously produced the antigen-specific antibodies, resulted in strong long-lasting immune responses with reduced dose schedules. Even different intervals between first and second doses also may affect immunogenicity response.

According to this, Director of Family Health Development Division, MOH requested an update on the HPV vaccine in order to look at the effectiveness, safety and cost-effectiveness in three scenarios; first was one-dose schedule compared to two-dose schedule of HPV vaccination among young girls at age of nine to 13 years-old, second was a long interval (>15 months) between first dose and second dose of HPV vaccine and third was two-dose schedule compared to three-dose schedule among women at age of more than five-years old.

Objective/ aim

The objective of this technology review was to assess the efficacy/effectiveness, safety and cost-effectiveness of HPV vaccination using three scenarios:

i. The HPV vaccine schedule for young girls (nine to 15-years old) is reduced to one-dose instead of two-dose which is currently being practiced in MOH
ii. The gap between first dose and second dose is extended up to more than 15 months. Currently the gap that is being practiced is 5 to 13-months apart
iii. The vaccine schedule for women aged of ≥15 years old is reduce to two-dose schedule instead of three-dose schedule

Results and conclusions:

Search results

A total of 383 records were identified through the Ovid interface and PubMed while three were identified from references of retrieved articles. After removal of four duplicates, 382 titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, 75 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria,16 studies were included while 59 were excluded since the studies were already included in systematic review and meta-analysis (n=7), irrelevant study design (n=32) and studies not addressing required HPV vaccine dose and vaccination schedule (n=20). Sixteen full text articles finally selected for this review comprised of four systematic reviews included one with meta-analyses, two RCTs, five non-RCTs, three cohorts, one post-hoc analysis and one economic evaluation. Data or trials included in the studies mainly from/in USA, Australia, Canada, Netherlands, India, Fiji, Vietnam and Uganda.

Vaccine Efficacy/Effectiveness

Single dose vaccination of 2vHPV showed no difference in efficacy towards HPV16 and HPV18 where the cumulative incidence for both HPV types at seven years was ranged from 1.5% (95%CI 0.2–5.3%) in the 1-dose arm to 4.3% (95%CI 3.5–5.3%) in the 3-dose arm. Similar efficacy was also observed with single dose of 4vHPV vaccine when compared before vaccination; the hazard ratio (HR) of HPV infection was significantly lower for all doses (1-, 2- and 3-dose) and remained equivalent for one-dose; (HR 0.47 [95% CI 0.38, 0.58]), 2-dose (HR 0.44 [95% CI 0.38, 0.51]) and 3-dose (HR 0.43 [95% CI 0.41, 0.45]). Although the GMTs level for single dose was lower compared to two- and three-doses, the seropositivity in single dose was as high as two- and three-dose which was 98.3% for HPV16 and 87.08% for HPV 18.

Then, while compared the efficacy of HPV vaccination at different dosing intervals either long or short interval; the included studies reported that in all HPV vaccine types, the GMTs level in longer interval was 2.5 to 5 times higher than short interval. Anogenital warts incidence rates also showed no significant difference among different intervals. The long interval was ranged at seven- to 12-months and the short interval was ranged at three- to six-months.

Only one RCT reported that 2-doses schedule in women aged 15 to 25-years old resulted in lower GMCs level than 3-doses schedule but the seropositivity was high in both groups.

Safety

Most of included studies reported that all HPV vaccine doses at any interval had comparable adverse events. The most common ADRs were pain (after HPV vaccine injection two-dose versus three doses; RR 0.96, 95% CI 0.91, 1.03), swelling (reduced in two-dose than three-dos; RR 0.76, 95% CI 0.65, 0.89) and redness (reduced in two-dose than three-dose; RR 0.85, 95% CI 0.75, 0.96) at injection site and nausea. No serious ADRs reported.

Organisational

Shortage in HPV vaccine supply worldwide may affect low-income countries (LIC) and low-middle income countries (LMIC) to fulfil the HPV vaccination programme. Thus, those countries required certain strategies including reducing the number of doses yet still had desired protection. In addition to that, other factors that may affect the completion of HPV vaccination especially in three-dose schedule were caregiver's educational level, and accessibility of immunization appointments.

Economic implication

One economic evaluation conducted in lower income country; Uganda was retrieved. The study simulated two scenarios; Scenario A that compared routine one dose HPV vaccination of nine-year-old girls starting in 2017 to no vaccination and Scenario B that compared routine one-dose HPV vaccination to two doses HPV vaccination of nine-year-old-girls. Overall, the cost-effectiveness of any doses will depend on the vaccination coverage observed within certain period. Although the one dose vaccination with higher coverage remained cost-saving regardless of waning assumption, two doses vaccination was considered 'very cost-effective' when one dose protection declines at 10 to 15 years.

Methods

Literature search was conducted by the author with help from Information Specialist who searched for full text articles pertaining to HPV vaccination. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 5th February 2021, EBM Reviews - Health Technology Assessment, EBM Reviews - Cochrane Database of Systematic Review (2005 to 5th February 2021), EBM Reviews - Cochrane Central Register of Controlled Trials (February 2021), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2016), and EBM Reviews - NHS Economic Evaluation Database. Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Additional articles were identified from reviewing the references of retrieved articles. The last search was performed on 5th February 2021.

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ABBREVIATION

AEs	Adverse events or adverse effects
AIS+	Adenocarcinoma-in-situ
$AS0_4$ ($Al(OH)_3$	Aluminium salt
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CIN2 or 3	Cervical Intraepithelial Neoplasia
CVT	Costa Rica Vaccine Trial
EMA	European Medicines Agency
HPV	Human Papilloma Virus
HR	Hazard Ratio
2vHPV	Bivalent HPV vaccine
4vHPV	Quadrivalent HPV vaccine
9vHPV	Nonavalent HPV vaccine
GMTs	Geometric Mean Titres
GMCs	Geometric Mean Concentrations
IARC Trial	India HPV Vaccine Trial
ICER	Incremental cost-effectiveness ratio
IgG G	Immunoglobulin G
IgG A	Immunoglobulin A
INFγ	Interferon Gamma
INAHTA	International Network of Agencies for Health Technology Assessment
MaHTAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
NAbs	Neutralising Antibodies
OR	Odds ratio
aOR	Adjusted odds ratio
PATRICIA Trial	PApilloma TRIal against Cancer In young Adults
PR	Prevalence Ratio
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Relative Risk
USA	United State of America
US FDA	United States Food and Drug Administration
WHO	World Health Organisation

1.0 BACKGROUND

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract in women and men. Persistent infections can lead to pre-cancerous lesions and cancer of the cervix, vagina, vulva, anus, penis and including head and neck. The International Agency for Research on Cancer classifies HPV genotypes according to oncogenic potential. The HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are considered as high-risk genotypes. On top of that, the HPV16 and HPV18 are the most common genotypes in women worldwide and are associated with most cases of invasive cervical cancer. As prevention, three prophylactic HPV vaccines are available. The vaccines are commonly known by the number of different genotypes that they contain. First, the bivalent vaccine (2vHPV vaccine) for the most common HPV genotypes; 16 and 18. Second, the quadrivalent vaccine (4vHPV vaccine) of four HPV genotypes; 16 and 18, plus HPV 6 and 11, which cause genital warts and the third HPV vaccine is nonavalent vaccine (9vHPV vaccine) that cover nine HPV genotypes; 6, 11, 16, 18, 31, 33, 45, 52 and 58.[1]

Harper D et. al. in their review acknowledged global reaction to HPV vaccination over the past decade. From the regulatory approval of the first HPV vaccine on June 2006, through October 2014, 68 countries and 12 territories adopted HPV vaccination program. Even, the World Health Organisation (WHO) recommended the use of two dose schedule, nine high income countries have continued follow-up of the female three dose HPV vaccine series: those countries were United State of America (USA), Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada and Germany. Seven years follow up; 2007 to 2014, it showed a population-level impact after female vaccination when the population vaccine coverage rates exceed 50%.[2]

The two-dose schedule recommended by WHO in a 2014 updated guideline was based on trials that found the two-dose schedule was as effective as the three-dose schedule.[3] In addition, there were studies reported that the structural characteristics of the virus-like particles of the vaccine allowed an efficient production of the long-lived plasma cells, which continuously produced the antigen-specific antibodies, resulted in strong long-lasting immune responses with reduced dose schedules. Other studies also determined that preadolescents and adolescents (age 9 to 15 years) would produce stronger antibody responses to virus-like protein HPV vaccines than older adolescents and adults, even after a single dose. Besides, different intervals between first and second doses also may affect immunogenicity response.[1]

Based on this, the Director of Family Health Development Division, MOH requested an updated review on the HPV vaccine in order to determine the effectiveness, safety and cost-effectiveness of HPV vaccine in three scenarios; first one-dose schedule compared to two-dose schedule of HPV vaccination among young girls at age of nine to 13 years-old, second was a long interval (>15 months) between first dose and second dose of HPV vaccine and

third was two-dose schedule compared to three-dose schedule among women at age of more than five-years old.

2.0 OBJECTIVE / AIM

The objective of this technology review was to assess the efficacy/effectiveness, safety and cost-effectiveness of HPV vaccination using three scenarios:

i. The HPV vaccine schedule for young girls (nine to 15-years old) is reduced to one-dose instead of two-dose which is currently being practiced in MOH
ii. The gap between first dose and second dose is extended up to more than 15 months. Currently the gap that is being practiced is 5 to 13-months apart
iii. The vaccine schedule for women aged ≥15 years old is reduced to two-dose schedule instead of three-dose schedule

3.0 TECHNICAL FEATURE

Currently, there are three HPV vaccines available.

i) Quadrivalent vaccine (Gardasil): First HPV vaccine authorised by the European Medicines Agency (EMA) in September 2006 for the European Union. The vaccine constituted of 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 aluminium salts (amorphous aluminium hydroxyphosphate sulphate).[4]

ii) Bivalent vaccine (Cervarix): Second HPV vaccine authorised in 2007. The vaccine constituted of an L1 surface antigen of the human papilloma viruses. Cervarix is a bivalent VLP vaccine consisting of serotypes 16 and 18, adjuvanted with aluminium salts $AS0_4$ ($Al(OH)_3$).

iii) Nonavalent vaccine (Gardasil 9): EMA authorised 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.[4]

World Health Organisation recommends HPV vaccination (any HPV vaccine) for girls in the age group of nine to 13 years old. Girls who receive first dose of HPV vaccine before 15 years old 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. 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 route.[4]

4.0 METHODS

4.1 SEARCHING

Literature search was conducted by the author and with help of an *Information Specialist* who searched for full text articles pertaining to HPV vaccination related to different dosage and schedule.

The following electronic databases were searched through the Ovid interface:

- MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 5th February 2021
- EBM Reviews – Health Technology Assessment
- EBM Reviews – Cochrane Database of Systematic Reviews – 2000 to 5th February 2021
- EBM Reviews – Cochrane Central Registered of Controlled Trials February 2021
- EBM Reviews - NHS Economic Evaluation Database

Other databases:

- PubMed
- Other websites: US FDA, INAHTA, CADTH

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 5th February 2021.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist* and graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). RoB 2 also used for the RCTs. Data were extracted and summarised in evidence table as in **Appendix 3**.
The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Girls at age of 9 -15 years old and women > 15 years old
b.	**Intervention**	HPV vaccination programme, 2vHPV, 4vHPV & 9vHPV (2-dose & 1-dose and >15 interval between 1st dose and 2nd dose)
c.	**Comparator**	i. Current practice (2-dose & 3-dose schedule and interval 5- to 15-months between 1st dose and 2nd dose)
d.	**Outcomes**	i. Immunogenicity (GMT, GMC) ii. Safety – adverse events iii. Cost-effectiveness – ICER, QoL etc
e.	**Study design**	Systematic review (SR), randomised controlled trials (RCTs), Pre- and Post- intervention study, cross-sectional study and cohort
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case-control, animal study
b.	Non-English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 1**. A total of **383** records were identified through the Ovid interface and PubMed while **three** were identified from references of retrieved articles. After removal of **four** duplicates, **382** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **75** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria,**16** studies were included while **59** were excluded since the studies were already included in systematic review and meta-analysis (n=7), irrelevant study design (n=32) and studies not addressing required HPV vaccine dose and vaccination schedule (n=20). **Sixteen** full text articles finally selected for this review comprised of four systematic reviews included one with meta-analyses, two RCTs, five non-RCTs, three cohorts, one post-hoc analysis and one economic evaluation. The studies analysed data or conducted trials mainly from/in USA, Australia, Canada, Netherlands, India, Fiji, Vietnam and Uganda.

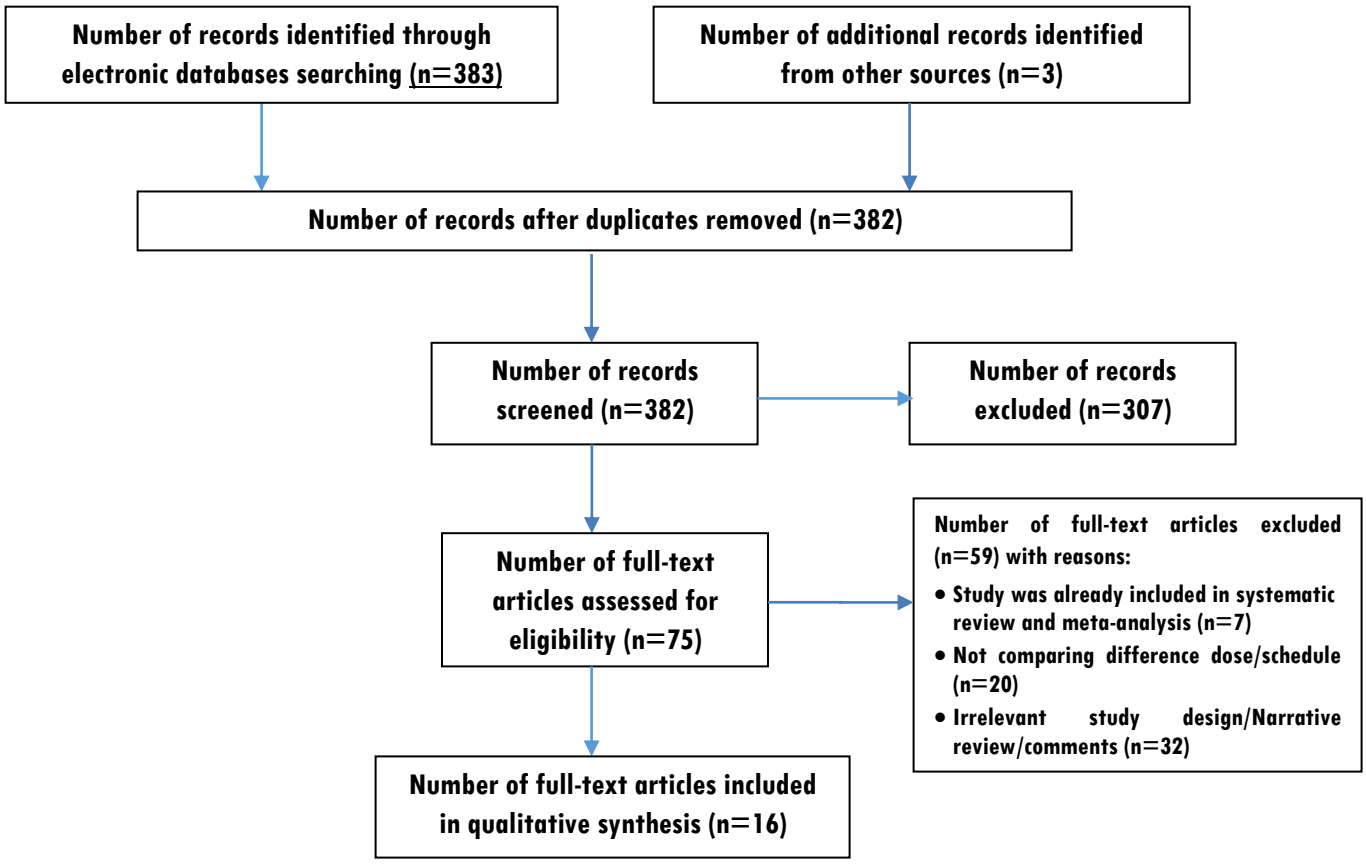

Figure 1: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias in the included studies were assessed using domain-based evaluation. Tools that are being used by MaHTAS to assess the risk of bias are adapted from the CASP checklist. 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:

Overall, the risk of bias was low for all included studies. The results of risk of bias of included studies are summarised in **Figure 2.1 and 2.4**

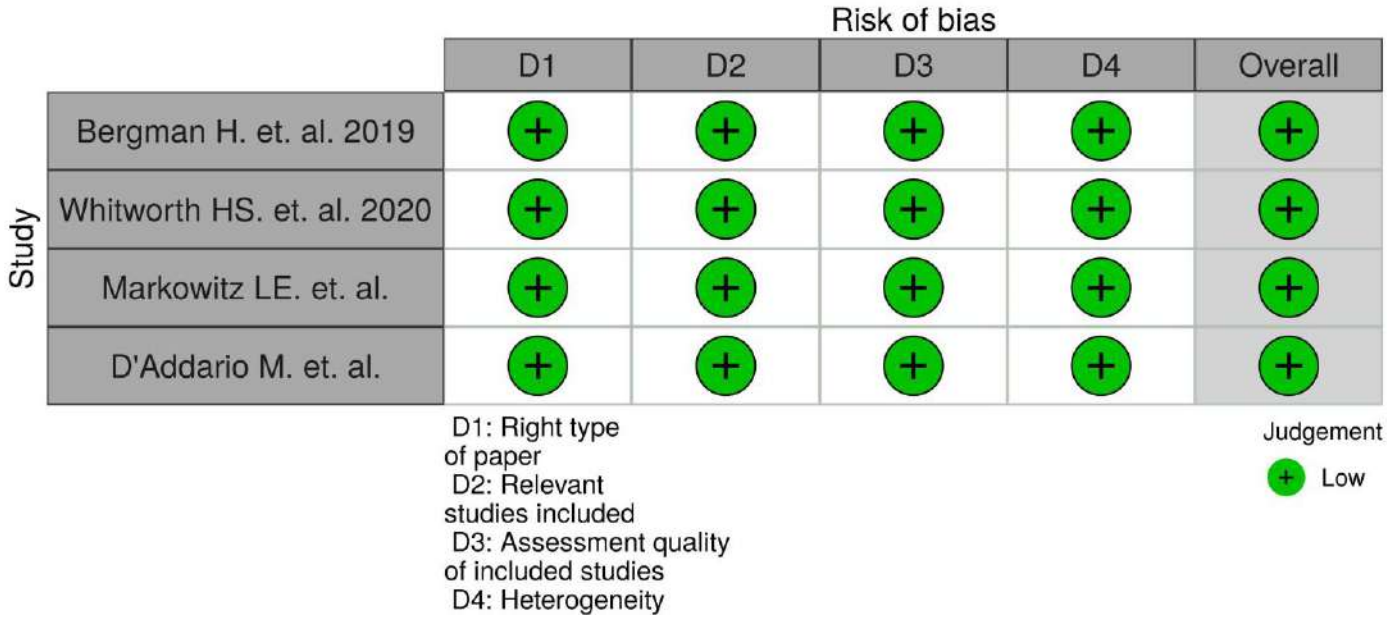

Figure 2.1 Assessment of risk of bias of systematic review (CASP)

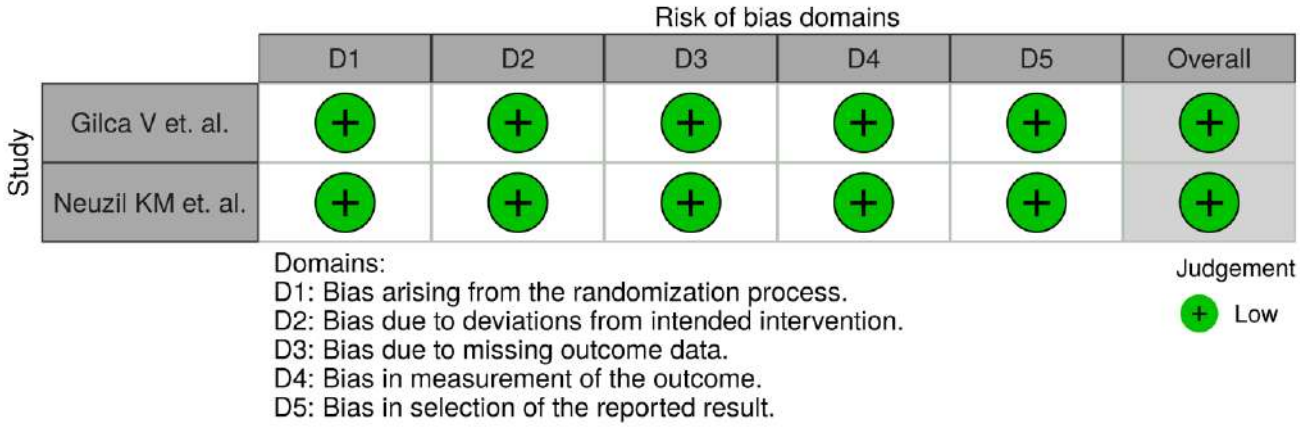

Figure 2.2 Risk of bias randomized controlled trial (Rob2)

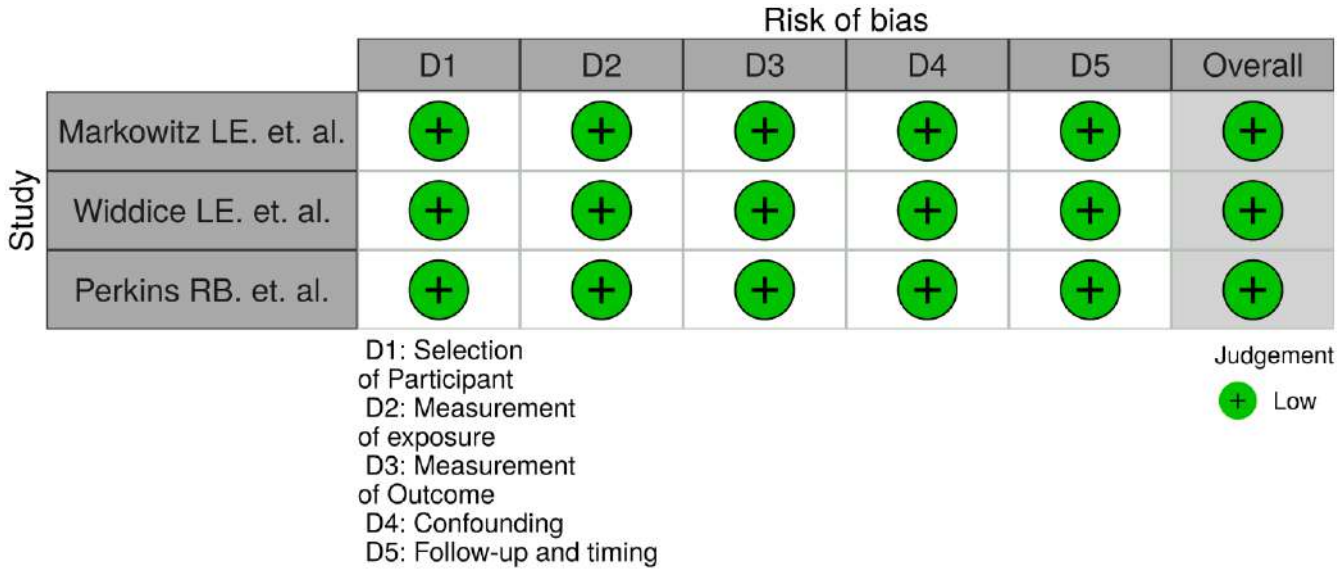

Figure 2.3 Assessment of risk of bias of cohort (CASP)

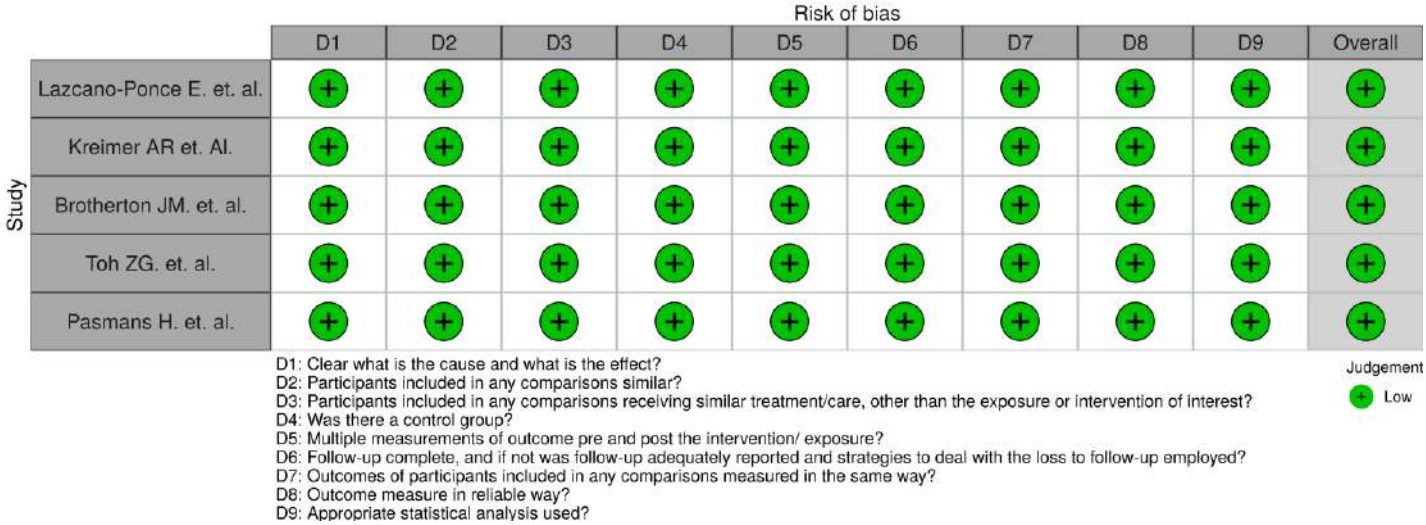

Figure 2.4 Assessment of risk of bias Non-RCT (CASP)

5.1 EFFICACY / EFFECTIVENESS

5.1.1 Immunogenicity and seropositivity

Cochrane SR by Bergman H. et al. in 2019 evaluated the efficacy, immunogenicity and harms of different dose schedules and different types of HPV vaccines in females and males. The SR reported, based on five groups; Group 1 assessed the effects of fewer than three doses of HPV vaccine in females and males, Group 2 assessed the effects of different intervals between doses in two doses schedule in females and males, Group 3 evaluated different intervals of HPV vaccination among males, Group 4 compared nonavalent HPV vaccine (9vHPV) and other HPV vaccines in females and males and Group 5 assessed the effect of HPV vaccination in HIV-positive females, males and men-sex-men. The SR included 20 RCTs with a total of 31, 940 participants. Nineteen RCTs was included in meta-analyses. The included studies used either 2vHPV vaccine, 4vHPV vaccine and 9vHPV vaccine. Overall length of follow-up in the included studies ranged from seven months to five years. Findings for Group 1 and Group 2 were simplified in the Table 1, and the findings for other groups can be referred to the Evidence Table in Appendix. For the immunogenicity and seropositivity findings, the results were described based on type of HPV covered regardless of vaccine type. [1, Level 1]

Table 1: Group 1 and Group 2 HPV vaccination

Groups/Outcomes	Outcome 1	
	Immunogenicity	**Level of Evidence**
i. Group 1 (2-doses vs 3-doses of HPV vaccine in 9- to 15-year-old females)	1 month after last dose of 9vHPV: • GMTs: 2-dose were non-inferior to or had higher GMTs than 3-doses for all 9 HPV genotypes measured except HPV45 • Ratio of GMTs 1.13 (0.99 to 1.29) reported in 1 SR • Seroconversion: little to no difference between groups for all 9 HPV genotypes measured At 36-month after 1st dose • 2 doses of 9-valent vaccine resulted in non-inferior GMTs for all HPV genotypes measured excepts HPV 45 and 52 After 60 months of 1st dose • Non-inferiority of 2 doses of 2-valent vaccine was inconclusive for GMTs of HPV 16 and -18 • 2 doses of 4-valent vaccine resulted in non-inferior GMTs for HPV 6, 11 & 16 and 18 inconclusive (low-certainty evidence)	Moderate to high certainty evidence High-certainty evidence High-certainty Low-certainty Low-certainty
ii. Group 2 (2-doses of HPV vaccine with longer interval compared with 2-doses of HPV	Interval 7-12 month (months 0 & 6 or 12) apart vs 3-6 months (months 0 & 2 or 6) At 1 month after final dose: ▪Higher (and non-inferior) GMTs for HPV-16 and -18 with	Moderate to high-

Groups/Outcomes	Outcome 1	
	Immunogenicity	**Level of Evidence**
vaccine with shorter interval in 9- to 14-year-old females or males)	longer interval schedules compared with shorter intervals (with 2vHPV) At 36 months after final dose: ▪Higher GMTs for HPV-16 and -18 with longer interval schedules compared to shorter intervals (with 2vHPV) For 9vHPV vaccine, longer interval produced higher and non-inferior GMTs than shorter interval for all HPV genotypes	certainty evidence High-certainty evidence High-certainty evidence

*GMT = Geometric Mean Titre

Another SR in 2020 by Whitworth HS et. al. reviewed the literature on efficacy of single dose HPV vaccination compared to no vaccination and multi-dose schedule among vaccines trials participants. Seven studies included in the SR were six nested observational studies where the participants were randomised to receive two or three doses in three large HPV vaccine trials (Costa Rica Vaccine Trial [CVT]), India HPV Vaccine Trial [IARC] and PATRICIA Trial) and one small RCT where 10 participants received either one or no vaccine dose. The vaccines were either 4vHPV vaccine or 2vHPV vaccine. In a study that compared HPV vaccine with Hepatitis A vaccine (HAV); the incident, persistent and prevalent infection with HPV16 and HPV18 were significantly lower than participants who were either unvaccinated or vaccinated with HAV. Besides that, all studies reported comparable efficacy against HPV16 and HPV18 infections in one, two or three dose arms. Frequency of HPV16/18 infection was low in all vaccinated participants up to seven years post vaccination and did not significantly differ by number of doses ($p > 0.05$ in all cases). Frequency of infection was significantly lower in one-dose recipients compared to unvaccinated controls ($p < 0.01$ for all infection endpoints in each study). HPV16/18 seropositivity rates were high in all HPV vaccine recipients (100% in three of four studies reporting this endpoint), though antibody levels were lower with one compared to two or three doses. Table 2 below showed the summary of HPV vaccine efficacy with different doses from the three large vaccine trials. For CVT, at 4 years the participants were at age of 22 to 29 years old. Meanwhile at 7 year of post vaccination, the participants were at age of 25 to 32 years old. For IAC trial, at 4 years the participants age was 14 to 22 years and at 7 years, the participants age was 17 to 25 years. Then for PATRICIA trial, at 4 years the participants age was 19 to 29 years old.[5, Level 1]

Table 2: Summary of HPV vaccine effectiveness at different doses from three trials

Trials / Dose/ length of Follow-up	At 4 Years: Persistent of HPV16 or HPV18			At 7 Years: Cumulative incident of HPV16 and HPV18		
	1-dose	2-doses	3-doses	1-dose	2-doses	3-doses
CVT Trial (2vHPV vaccine)	100% (95% CI 66.5, 100)	84.1% (95% CI 50.2, 96.3)	80.9% (95% CI 71.1, 87.7)	Ranged from 1.5% (95%CI 0.2–5.3%) in the 1-dose arm to 4.3% (95%CI 3.5–5.3%) in the 3-dose arm		
IARC Trial	No persistent HPV 16 or 18 infections were			1.6%	0.9% (95%CI	0.9% (95%CI

(4vHPV vaccine)	detected in any of the dosage groups (1, 2 or 3 doses) of post vaccination with 4vHPV			(95%CI 1.1, 2.3)	0.5, 1.7)	0.5, 1.7)
PATRICIA Trial	76.8% (95% CI 118, 99.1)	100% (95% CI 60.7, 100)	88.2% (95%CI 84.6, 91.0)	-	-	-

In terms of seroconversion of HPV16 and HPV18 antibody, four included study compared one dose of HPV vaccine with other type of vaccine dosage schedules. The proportions of participants who were seroconverted to HPV16 and HPV 18 antibody-positive were generally high in all HPV vaccine arms. Although the antibody levels were significantly lower in one-dose than two and three doses, the levels for two- and three-doses arms declined following the initial increase and plateau thereafter but was less pronounced in one-dose group as the level remained stable throughout follow-up.[5, Level 1]

Markowitz LE et. al. conducted an SR in order to summarise evidence about the effectiveness of HPV vaccination by the number of doses, as measured in post-licensure studies and also to explore and discuss the main limitations and challenges of these studies. Fourteen studies form Australia, Scotland, United States, Sweden, Belgium, Canada, Denmark and Spain was included in the SR. Out of 14 studies; three studies were on 2vHPV vaccine and 11 studies were on 4vHPV vaccine. The authors classified the included studies on the effectiveness of HPV vaccine for prevention of HPV infections (two studies), anogenital warts (six studies), and cervical cytological or histological abnormalities (six studies). The overall findings for HPV vaccine effectiveness, 2 studies reported that 3-doses of 2vHPV vaccine was statistically significant compared to 2-doses and 1-dose. The adjusted odd ratio (aOR) in those were aOR = 0.43 (95% CI 0.34, 0.55) and aOR = 0.27 (95% CI 0.20, 0.37), respectively.[6, Level 1]

One SR with MA conducted by D'Addario M. et. al. described the adoption of 2-doses HPV vaccination schedules. The review included adults over 15 years old as the inclusion criteria. Seven trials were included in the SR, all of which used a non-inferiority trial design; six trials reported on 11 eligible comparisons between groups of adolescent girls or compared adolescent girls and women; and one trial compared schedules between groups of women. The trials were conducted in 11 countries: two trials in high income countries only (Canada and Germany), two trials in both high- and middle-income countries (Canada, Germany, Italy, Romania, Slovakia, Taiwan, Thailand), two in middle income countries only (India, Mexico), and one in low-income countries only (Senegal and Tanzania). The updated search did not identify any new trials but found additional results for two trials (Canada/Germany1, Multinational 2) and results from second arm of a previously included trial in Mexico. Two types of HPV vaccine were assessed in the SR; 2vHPV vaccine and 4vHPV vaccine. First finding was on two-dose versus three-dose schedules in adolescent girls (9 – 14 years old) as primary population compared with women aged over than 15 years old. After one month of last dose the Canada1 trial showed that for the two-dose schedule the GMC level for HPV16 was non-inferior to the three-dose schedule and inconclusive in the Canada/Germany1 trial as for HPV18, both trials showed that the GMCs in the two-dose group were lower, but non-

inferior to those in the three-dose group. Meanwhile in India, the GMCs level were higher in the two doses group for both HPV16 and HPV18. At later time points (at 36-, 48- and 60-months), the GMCs level for HPV16 or HPV 18 were lower in girls who received two-dose than those who received three-dose. Second findings were on two-dose schedule HPV vaccine in girls versus three-dose schedule HPV vaccine in women. The results showed that the GMCs level in girls who received two-dose prime-boost schedule were higher than women who received three-dose schedule. The combined pooled GMCs ratios for HPV16 was 1.44 (95% CI 1.04, 2.00) and for HPV18 was 1.52 (95% CI 1.25, 1.84). On the other hand, trials with longer follow-up showed that non-inferiority was maintained up to 48 months after the 1st dose. Another observation was on 2-dose schedules at different intervals between doses: the included trials showed that GMCs was higher as the interval between doses was longer (12-months interval). One RCT reported that 2-doses schedule in women aged 15 to 25-years old resulted in lower GMCs level than 3-doses schedule but seropositivity was high in both groups.[7, Level 1]

Gilca V et. al. conducted an RCT to evaluate the immunogenicity and safety of two doses of 9vHPV vaccine versus one dose of 2vHPV vaccine. The trial was conducted in Quebec City, Canada where 371 healthy girls and boys aged 9 to 10-years old were included. The participants were randomised twice. In the first randomisation, 184 of the participants were allocated to receive 2-doses of 9vHPV (Group 1) and another 187 participants received a mixed schedule of 1 dose of 9vHPV and 1 dose of 2vHPV vaccine (Group 2). The second randomisation allocated the participants in the first group to either one month or six months of post-first dose blood sample collection time. Meanwhile for Group 2, patients were randomised to receive 9vHPV and 2vHPV vaccine in different order either [9vHPV + 2VHPV] or [2vHPV + 9vHPV]. Per protocol interval between dose was six-months. First blood sampling was 28 to 38 days post-first dose of two-dose 9vHPV vaccine and at 173 to 202 days post-first dose of one-dose 2vHPV vaccine. Second blood sampling was 11 to 45 days post-second dose of vaccination. In post-first dose of 9vHPV vaccine, all subjects were seropositive to all vaccine HPV types except one subject (0.6%) was negative to HPV45. Besides that, there was no difference in seropositivity or antibody GMTs was observed between subjects who were tested at one or six month post-first dose vaccination ($p > 0.05$). The GMTs level were varied ranged from 4.6 to 75.1 IU (AU)/ml. As for immune response to the first dose of 2vHPV vaccine, all subjects were seropositive to HPV16 and HPV18 at six-months post vaccination. The GMTs level was 16.7 IU/mL for HPV16 and 11.7 IU/ml for HPV18. As for second dose immune response, irrespective of vaccination schedule, after one month of second dose vaccination, all subjects were seropositive to the nine HPV types. Compared to the GMTs level of post-first dose's vaccination there was a statistically significant 1.3 to 143-fold increase in antibody GMTs after the second dose in all study groups for all nine HPV types except for HPV11 in the 9vHPV + 2vHPV group [Group 2] (1.2-fold GMT increase; $p = 0.008$). Among those who received two different vaccines, the GMTs to HPV16 were higher when 2vHPV vaccine was the first dose and the GMTs to HPV6, 11, 31, 33, 45, 52 and 58 were higher in subjects who received doses of 9vHPV vaccine.[8, Level 1]

Neuizil KM et. al. conducted an RCT to determine the immunogenicity and reactogenicity of different three-dose schedules of 4vHPV vaccine in adolescent in Vietnam. The trial involved 903 girls at age of 11 to 13-years old. The trial was conducted between October 2007 and January 2010. Those girls were randomised to four vaccination schedules; standard schedule (three-dose at 0, 2 and 6 months) and three alternative dosing schedules which were three-dose at 0, 3 and 9 months, three-dose at semi-annual schedule (0, 6 and 12 months) and three-dose at annual schedule (0, 12 and 24 months). Out of 903 participants recruited, 809 girls (89.6%) received all three doses and had a serum sample available for testing after final dose of HPV vaccination. Besides that, almost all participants in semi-annual group and annual group received the measles vaccine 12 to 27 days prior to the first HPV vaccine dose. For all vaccination schedules, the HPV GMTs were low at baseline and increased significantly after the third dose of the HPV vaccine. In intention-to-treat (ITT) population and compared with the standard schedule, the alternative schedule of 0, 3 and 9 months and the semi-annual group met the non-inferiority criteria for the anti-HPV16 and anti-HPV 18 one month after receipt of the third vaccine dose. Meanwhile the annual schedule group met non-inferiority criteria only for anti-HPV18. However, after adjustment for baseline characteristics of age, ethnicity and urban or rural residence, the results were similar among the groups. The overall results of ITT were simplified in table below. The per protocol results also similar as ITT findings.[9, Level 1]

Table 3: The overall results of Intention-to-treat in all groups

Group	Schedule (months)	GMTs level for HPV Types (ITT)			
		HPV6	HPV11	HPV16	HPV18
Group 1: standard	0, 2 and 6 months	988.3 (95% CI 832.2,1173.7)	1610.0 (95% CI 1433.6, 1808.1)	5808.0 (95% CI 4961.4, 6799.6)	1729.9 (95% CI, 1504.0, 1989.7)
Group 2	0, 3 and 9 months	1086.6 (95% CI 922.2,1280.4)	1383.2 (95% CI 1227.2, 1559.1)	5368.5 (95% CI, 4632.4,6221.5)	1502.3 (95% CI, 1302.1,1733.2)
Group 3: semi-annual	0, 6 and 12 months	1116.9 (95% CI 940.1, 1326.9)	1382.1 (95% CI 1212.4, 1575.6)	5716.4 (95% CI 4876.7, 6700.6)	1581.5 (95% CI 1363.4, 1834.6)
Group 4: annual	0, 12 and 24 months	647.2 (95% CI 521.8, 8802.7)	1550.4 (95% CI 1406.4, 1709.0)	3692.5 (95% CI 3145.3, 4334.9)	13357 (95% CI 1191.6, 1497.3)

Lazcano-Ponce E et. al. conducted an open-label non-RCT clinical trial to evaluate the immune response to the HPV-16/18 of 2vHPV vaccine administered on a standard schedule (0, 1 and 6 months) versus extended schedule (0, 6 and 60 months) at 7-, 21-, 60-, 72- and 120-month post-post vaccination. A total of 2000 participants were enrolled and 1,500 girls at age of 9 to 14 years old received HPV vaccination (474 received standard three-dose schedule [Group 1] and 1,026 were assigned with extended schedule (currently the girls in the extended schedule had received only the first 2 doses) [Group 2]). Another 400 participants were women aged 18 to 24-years old who received standard three-dose vaccination schedule (Group 3). All participants in the two-dose group (Group 2) received the vaccine at months 0 and 6 within a 12-month period, and 82% of them received both doses within 9 months. Meanwhile, 94% of the girls and women in the three-dose group (Group 1 and Group 3) received the complete regimen within 9 months. Antibody levels of HPV-16 and

HPV-18 were assessed in a random sample of 100 sexually active women aged 18–24 years: 74% of the women were seronegative at baseline for HPV-16 antibodies and 94% were seronegative at baseline for HPV-18 antibodies. At the end of the study, the results showed that all participants were seropositive for both HPV16 and HPV18 antibodies at months seven and 21. Among the total vaccinated cohort, antibody titres at month seven ranged from 529 to 268,239 for HPV-16 and from 43 to 143,989 for HPV-18. The antibody levels achieved at month 21 ranged from 90 to 29,386 for HPV-16 and from 17 to 12,965 for HPV-18. The authors also observed that the distribution of HPV16 and HPV18 antibodies titres of participants in Group 2 and Group 3 were shifts towards the lower quintiles. At month 21, a large proportion (63.4%) of women in Group 3 were within the lowest quintile of anti-HPV16 of the reference group, while only 1.7% of this group have comparable levels to those in the top quintile. The Group 2 also tended to have lower antibody levels, but was more homogenous across the quintile values defined by the reference group distribution; 43% were in the lower quintile and close to 11 were in the higher quintile. The GMTs for HPV16 and HPV18 antibodies in 21 months after first vaccine dose in the Group 2 were higher and statistically non-inferior to those in the Group 3 because the upper limit of the 95% CI of the GMT ratio was below the predefined limit of 2.0. When comparing between Group 1 and Group 2, the antibody level was higher in Group 1 but the levels for those who received two dose HPV vaccine (Group 2) were statistically non-inferior. The antibodies levels against HPV16 and HPV18 in Group 2 followed similar pattern to that observed in the other two groups after a peak response at month seven. However, a decline in antibody titres was observed at month 21.[10, Level II-1]

Brotherton JM et. al. conducted cohort study to determine the effectiveness of 4vHPV vaccine by number of doses against CIN2 or 3/adenocarcinoma-in-situ (AIS)/ cancer in Australia up to 7 years post vaccination. The cohort was based on screening cohort of young women who were vaccinated at an age at which they were predominantly HPV naïve. the study period was defined as 1 April 2007 until December 2014. The cohort involved 250,648 women where 19.5% (48,845) were unvaccinated, 69.85% (174,995) were those who received 3-doses, 7.3% (18,190) received 2-dose and 3.4% (8,618) received 1-dose of 4vHPV vaccine. Thus, for the purpose of the study, the authors assigned the dose status to women using their final dose status either zero dose, one dose, two doses or three doses. In order to avoid biased findings (by assigning prevalent disease to earlier doses in the vaccine course), the authors determined the outcomes for the vaccinated women only after their final dose which was after they had their first screening during the vaccination course. In order to avoid a systematic bias, the authors excluded unvaccinated women who commenced screening prior to age 16. After those considerations, the authors reported that the incidence of CIN2/AIS+ was highest among unvaccinated women (13.2 per 1000 women) and reduced by vaccination; 1-dose the rate was 10.3 per 1000 women, 2-dose the rate was 9.5 pre 1000 and 3-dose was 8.5 per 1000. The adjusted hazard ratio (HR) also significantly lower and comparable between the vaccine dose groups compared to unvaccinated women; 1-dose (0.65 [95% CI 0.52, 0.81]), 2-dose (0.61 [95% CI 0.54, 0.65)] and 3-dose (0.59 [95% CI 0.54,

0.65]). The effectiveness of vaccination by number of doses over time against CIN2/AIS+ indicated that some initial differences by vaccination status but a clear convergence over time between the cumulative incidence rate in unvaccinated compared to vaccinated women; regardless of number of HPV vaccine doses, $\chi = 126.76$, $p < 0.0001$. When incidence in a pre-vaccination cohort (270, 613) was compared, herd protection of unvaccinated women became apparent; HR 0.73 [95% CI 0.67, 0.79]). When the pre-vaccinated group was used as a comparator, HR were significantly lower for all groups and remained equivalent for 1-dose (HR 0.47 [95% CI 0.38, 0.58]), 2-dose (HR 0.44 [95% CI 0.38, 0.51]) and 3-dose (HR 0.43 [95% CI 0.41, 0.45]).[11, Level II-1]

The non-RCT study by Kreimer AR. et. al. was to summarise the evidence for single-dose efficacy of the 2vHPV vaccine from post-hoc analysis of the Costa Rica Trial (CVT). The CVT was phase III RCT held in 2004 to 2005 with a total of 7,466 women were randomised to receive either 2vHPV vaccine or hepatitis A vaccine (HAV) as a control in 1:1 ratio at 0-, 1- and 6-months. The participants were followed annually for four years. At the end of the trial, the participants were offered the vaccine they had not received at enrolment (cross-over vaccination) and were invited to stay in a long-term followed-up observational study. The follow-up was conducted biennially for six additional years. The original control group was replaced with 2,836 unvaccinated women who were recruited from the same birth cohorts and geographic regions as the original trial's participants. The antibody levels were measured at one-month following the initial dose administered in all groups irrespective of the total number of doses the participant should receive and the results showed no significant difference between groups. In evaluation of single-dose efficacy of 2vHPV vaccine, the data were assessed at two time points; at four years and at seven years. At 4 years after initial vaccination, single dose of 2vHPV vaccine had comparable efficacy to three doses of 2vHPV vaccine using an endpoint of cumulative persistent HPV infection. The four-year efficacy against HPV16 or HPV18 infections (that persistent for at least six months) among women who were HPV DNA negative for these types at first vaccination was 81% (95% CI 77, 89%) for three doses, 81% (95% CI 53,94%) for two doses and 100% (95% CI 79,100%) for one dose. Then, the 4-year efficacy against endpoint of cumulative incidence HPV16/18 infection hovers around 80% for all dose groups which showed that one dose HPV vaccine efficacy was not inferior to three doses vaccine efficacy among the same analytic population and utilized the same endpoint for analyses. On the other hand, in seven-years observational study, strong protection was observed with a single dose of the 2vHPV vaccine indicated no evidence of diminishing. Besides that, among single dose participants, there was no HPV16 and HPV18 cervical infections detected at year seven. The results were also similar as in three doses participants. For comparison, the HPV prevalence among the unvaccinated women was considerably higher for HPV16 and HPV18 (6.6%), suggesting that even a single dose continued to provide robust protection. The authors also observed the serum antibody patterns at four-years and seven-years. At four-years, 100% participants who received single dose of 2vHPV vaccine were seroconverted to HPV16 and HPV18 antibody. After seven-

years of post-vaccination the antibody titres remained stable and elevated but four- to five-fold lower than the two or three doses.[12, Level II-1]

Toh ZG et.al. conducted a non-RCT to determine whether girls who were vaccinated previously with one or two doses of 4vHPV in 2008 or 2009 had similar immune responses to girls who received three doses and to evaluate the effect of one-dose of 2vHPV vaccine in the same groups of girls. The study was conducted in Fiji between February and March 2015. The authors obtained the immunisation records of 4vHPV vaccine campaign in 2008/2009 from Fiji's Ministry of Health and the girls recruited were from listed patients who had previously received one, two or three doses of 4vHPV vaccine. Control participants who did not receive any prior 4vHPV vaccine were recruited by recommendation of friends of recruited girls and by informal network. A total of 200 girls participated; 66 girls in three doses group, 60 girls in two doses group, 40 girls in one dose group and 34 girls in zero dose group. The seropositivity in each group for HPV types six years after the last dose of 4vHPV were simplified in Table 4 below:

Table 4: Seropositivity of HPV types after 6years of 4vHPV vaccine last dose

Dose Group/HPV types	Seropositivity			
	0-dose	1-dose	2-dose	3-dose
HPV6	0%; n=0	90%; n=36	93%; n=56	100%
HPV11	0%; n=0	93%; n=37	93%; n=56	100%
HPV16	6%; n=2	95%; n=38	100%; n=60	100%
HPV18	3%; n=1	68%; n=27	90%; n=54	88%; n=58

The result showed that the highest neutralising antibody (NAb) titres in dose response towards 4 HPV types were observed in three, two and one dose groups. There were also no significant differences in GMT across all four HPV types between girls who previously received two or three doses of 4vHPV vaccine; HPV6; P = 0.074, HPV11; P = 0.086, HPV16; P = 0.887 and HPV18; P = 0.885. However, for girls who received one dose of 4vHPV vaccine had significantly lower GMTs for all four HPV types compared with girls who received two or three doses, but their NAb titres for all four HPV types were still five- to 30-fol higher than unvaccinated girls. The authors also assessed the difference in immunological memory following reduced-dose HPV schedules by administering a dose of 2vHPV vaccine to all girls in the study. The result showed that the NAbs titres in one-dose group was 46-fold increased for HPV16 and 84-fold increased for HPV18 to a level that was not significantly different between two-dose and three-dose group. On the other had the NAbs level for HPV6 and HPV11 were not significantly different after a dose of 2vHPV vaccine in all groups. Then, to look at the impact of dosing interval between the first and second dose of 4vHPV vaccine, the authors stratified girls in the two doses group into those who received second dose less than six months or six months above after the first dose. The study showed that no significant differences were seen for all 4 HPV types before or after the 4vHPV vaccine dose.[13, Level II-1]

Markowitz LE et. al. conducted another cohort study to evaluate the 4vHPV vaccine effectiveness by number of doses against 4vHPV-type infection. The study involved 4,269 women who were continuously enrolled from 30 June 2006 in the integrated healthcare delivery system. Cervical specimen from each participant was collected after a few years of enrolment. The age of those women at time of specimen collection were 20 to 29 years-old. From the sample, the study determined the prevalence of HPV infections based on the HPV types. The percentage and prevalence ratio (PR) of 4vHPV vaccine-types in those who received at least one-vaccine dose was 1.1%, and in unvaccinated women was 7.4% (PR = 0.14; 95% CI 0.10, 0.21). On the other hand, the 4vHPV-type prevalence among those who received the first dose at ≤18 years was 0.5% (PR = 0.07; 95% CI 0.04, 0.12) and among those who received the first dose at >18 years the prevalence was 4.6% (PR = 0.62, 95% CI 0.69, 1.01). When compared with unvaccinated women, the prevalence of 4vHPV vaccine-type was significantly lower among vaccinated women who received the first dose at ⩽18 years if they received the following doses: one-dose, 0.5% (PR = 0.07; 95% CI, 0.01, 0.47); two-dose, 0.4% (PR = 0.06;95% CI, 0.01,0.42); or three-dose, 0.5% (PR = 0.07; 95% CI, 0.04,0.1). However, when compared with the women who received the first dose at >18 years with unvaccinated women, although the prevalence of 4vHPV vaccine-type was lower than among unvaccinated women, the differences in all doses were not significant. The authors also compared the PR between difference doses; there were no significant difference overall limited to women who received the first dose at ≤18 years: 3-doses versus 1-dose, PR = 1.06 (95% CI, 0.14, 8.09); 3-doses versus 2-doses, PR = 1.17 (95% CI 0.15, 8.96) and 2-doses versus 1-dose, PR = 0.90 (95% CI 0.06, 14.36).[14, Level II-2]

Pasmans H et. al. conducted a non-RCT to observe seropositivity and to compare the B-cell and T-cell immunity following one-, two- and three-doses of 2vHPV vaccination as well as cross-reactive HPV types 31 and 45. Blood sampling was obtained from several studies and were collected over seven consecutive years following a one-, two- or three-doses of the 2vHPV vaccine. The Dutch national vaccination registry Praeventis was used to select the participants that had been vaccinated with the 2vHPV vaccine. One-dose 2vHPV-vaccine vaccinated girls were vaccinated between 2011 and 2016, two-dose 2vHPV-vaccine vaccinated girls were vaccinated between 2010 and 2013 and three-dose 2vHPV-vaccine vaccinated girls were vaccinated between 2009 to 2010. A total of 890 girls, between 13 and 21 years-old at time of sampling involved in the study. Among those included: 239 girls received one dose, 222 girls received two-doses and 378 girls received three-doses of the 2vHPV vaccine. For control, 51 unvaccinated girls were included. According to the results, specific antibodies levels of HPV16 and HPV18 in one-dose vaccinated girls were significantly lower than those in two-dose and three-dose vaccinated girls at all-time points but remained stable over seven years. For seropositivity, all girls who were vaccinated with two doses and three doses schedule were seropositive for both HPV16 and HPV18. Meanwhile, in one-dose vaccinated girls the seropositivity of the HPV16 was detected in 98.3% girls and 87.06% of vaccinated girls were seropositive to the HPV18. The level of the

specific antibody concentrations of HPV16 and HPV18 in one-dose group that stayed above an arbitrary level of 100LU/mL was 64.4% and 46.7%, respectively.[15, Level II-1]

Gilca V. et. al. conducted post-hoc analysis to compare the anti-HPV GMTs and the distribution after six months or a three- to eight-years interval between two HPV vaccine doses. The authors compared the results from two clinical trials which also being conducted by the authors previously. First study (Study A) involved 173 participants which included 88 girls and 85 boys who received two doses of 9vHPV vaccine at a six-months interval. The second study (Study B) was 31 girls who received one dose of 4vHPV vaccine at the age of nine- to 14-years old and another one dose of 9vHPV vaccine after three- to eight- years of the first dose. In both studies, the blood samples were collected before and one month after second-dose. At post-first dose vaccination the anti-HPV6, -HPV11, and -HPV16 in both studies were comparable. Meanwhile, for anti-HPV18, the GMTs level were higher in Study A where the subjects received 9vHPV vaccine as the first dose and were tested one- to six-months later ($p = 0.005$). The GMTs titres distribution also comparable in both studies. After the second-dose, all subjects were seropositive to HPV6, HPV11, HPV16 and HPV18. Both studies also showed an increment in GMTs level one month after second dose; 40- to 91-fold for those with a six-months interval (Study A) and 60- to 82-fold for those with a three- to eight-years interval.[16, Level II-2]

Widdice LE et. al. conducted a multi-site prospective cohort study to compare immunogenicity one month after completing the three doses vaccination series when the second and / or third vaccination dose was received after substantially prolonged intervals to those who received second and third dose within or close to the recommended intervals. There were 1,321 participants involved and they were divided into five groups as shown in Table 4. The eligible girls were enrolled either on the day of or prior to receiving their third 4vHPV vaccine dose or up to 28 days after receipt of dose three. Participants were assigned to a study group defined by the intervals between booster doses. The intervals were calculated from dates of vaccination obtained from clinical medical records and patient's immunization cards. The antibody responses after one month and six months of dose three for each group were summarised in Table 5. On the effect of delaying dose 2, a total of 390 participants (192 in Group 1 and 198 in Group 3) were seropositive for all four HPV types as measured before dosage 3 which was approximately four months after dose 2. However, post-dose 2 in Group 3 were non-inferior to Group 1 with GMTs 2.5 to 5 times higher in Group 3.[17, Level II-2]

Table 5: Antibody response after 1- and 6-months of dose three

Groups	Group Description	Antibody Response 1-Month After Dose 3	Antibody Response 6-Months After Dose 3
Group 1 (Control)	n = 224 On-time both dose 2 and 3 (within 51-70 days of dose 1 and 106-137 days of dose 2)	• All participants were seropositive to all 4 HPV types	• Participants were seropositive to all 4 HPV types • GMTs for each HPV type had decreased to less than 1-half the titres observed at 1 month

Groups	Group Description	Antibody Response 1-Month After Dose 3	Antibody Response 6-Months After Dose 3
Group 2	n = 173 On-time dose 2 but substantially later for dose 3 (≥ 240 days after dose 2)	• All participants were seropositive to all 4 HPV types • GMTs for HPV 6, 11, 16, and 18 in groups 2–4 was non-inferior to the control group. • Titres for HPV 6, 11, 16, and 18 were significantly higher than the control group	• Participants were seropositive to all 4 HPV types • GMTs for each HPV type had decreased to less than 1-half the titres observed at 1 month • Titres for HPV6, HPV11, HPV16 and HP18 were higher than and non-inferior to the control group • Titres for HPV 6, 11, and 16 were superior to the control group • Titres for HPV 18 were also superior compared to controls. • Highest HPV titres for each HPV type compared to other study groups.
Group 3	n = 222 Substantially late dose 2(≥ 120 days after dose 1), on-time dose 3	• All participants were seropositive to all 4 HPV types • Titres for HPV 11 in were significantly higher than the control group	• Participants were seropositive to all 4 HPV types • GMTs for each HPV type had decreased to less than 1-half the titres observed at 1 month • Titres for HPV6, HPV11, HPV16 and HP18 were higher than and non-inferior to the control group • Titres for HPV 6, 11, and 16 were superior to the control group
Group 4	n = 235 Substantially late for both dose 2 and dose 3	• All participants were seropositive to all 4 HPV types	• Participants were seropositive to all 4 HPV types • GMTs for each HPV type had decreased to less than 1-half the titres observed at 1 month • Titres for HPV6, HPV11, HPV16 and HP18 were higher than and non-inferior to the control group • Titres for HPV 6, 11, and 16 were superior to the control group • Titres for HPV 18 were also superior compared to controls
Group 5	n = 467 Participants receiving doses at intervals not included in the groups described above	• All participants were seropositive to all 4 HPV types	• Participants were seropositive to all 4 HPV types

5.1.2 Cross-Protection

Gilca V. et. al also reported on cross-protection effect in their RCT. The cross-protection on seven other HPV types that were covered under 9vHPV vaccine was seen in Group 2 as the second dose given was one dose of 2vHPV vaccine. It was found that the 2vHPV vaccine were seropositive to the seven other HPV types ranged between 50% to 76% with GMTs level ranged from 0.3IU/ml to 7.9IU/ml.[8, Level 1]

The non-RCT by Kreimer AR et. al. also assessed the cross-protection against vaccine-related types HPV 31/33/45. The authors stated that, in their initial assessment in a pooled analysis of the CVT and PATRICIA trial, after four years of follow-up, the cross protective efficacy was assessed among all women after excluding those who were HPV DNA-positive for HPV31/33/45 infections at the enrolment visit. The vaccine efficacy against one-time detection of HPV31/33/45 infection was as follows; 59.7% (95% CI 56.0, 63.0%) in 3-doses of 2vHPV, 37.7% (95% CI 12.4, 55.9%) in 2-doses of 2vHPV and 36.6% (95% CI -5.4, 62.2%) in 1-dose of 2vHPV vaccine. Further observation by classifying the cross-protection effect by the time of the second dose vaccine, the authors found that no vaccine efficacy towards HPV31/33/45 in women who received their second 2vHPV dose one month after the first dose. However, there was higher efficacy estimated in women who received their second dose six months after the first 2vHPV dose. In addition, seven-years analysis of CVT trial data showed that, the prevalence of HPV31/33/45 were similar between three doses, two doses and one dose groups; P=0.77. However, cross-protection towards HPV31/33/45 in single-dose require further assessment.[12, Level II-1]

In a cohort study by Markowitz LE et. al. the authors stated the overall prevalence of other HPV-types which was not covered under 4vHPV vaccine was 38.9%. Nevertheless, based on ethnicity the prevalence was higher in non-Hispanic black (49.8%) compared to non-Hispanic white (39.0%) and lower among Asians (25.9%). Similar findings were also observed in any high-risk HPV type. For HPV-31, -33 and -45, there was some variation by race/ethnicity with significantly lower prevalence among Asians compared to non-Hispanic white. However, the effectiveness towards HPV-31, 33 and -45 was not significant. In addition, as the 4vHPV vaccine covered four main HPV-types, the prevalence of the non-4vHPV vaccine-types were higher in those who were vaccinated with 4vHPV vaccine compared to unvaccinated women (40.4% versus 34.0%; PR =1.19 95% CI 1.08, 1.31).[14, Level II-2]

Pasmans H et. al. reported in their study, the cross-protection on non-vaccine-types antibody level towards HPV33, 34, 45, 52 and 58 were significantly lower in one-dose vaccinated girls compared to two- and three-dose vaccinated girl.[15, Level II-1]

5.1.3 Anogenital warts protection

The SR by Markowitz LE et. al. observed the effects of different dose of 4vHPV vaccine towards anogenital warts. While compared with no dose; all 3-doses, 2-doses and 1-dose of 4vHPV vaccine showed significant difference in reducing anogenital warts. The highest effectiveness was found in 3-doses than other doses (adjusted relative risk [aRR] = 0.20 95% CI 0.17, 0.23). At different intervals (four to seven months) in either 3-dose or 2-dose schedule, the authors found no significant difference in the incidence of anogenital warts reported in the included studies.[6, Level II-2]

Perkins RB et. al. conducted another cohort study to compare the relative protection afforded by unvaccinated, one-, two-, and three-doses of HPV vaccination against genital warts. The study included girls aged 9-18 years-old on 1/1/2007 and were continuously enrolled in the database from 1/1/2007 to 12/31/2013. The exposure period began on 1/1/2007 and ended when a subject either received a diagnosis of genital warts or at the end of the study period (12/31/2013). Since the early study, a vaccination distribution was as follows; 52% of girls remained unvaccinated, 7.8% received one-dose vaccination, 9.4% received two-doses and 30.7% received three-doses vaccination. At the end of the study, the authors reported the overall rate of genital warts was 197/1000 person years. The rate decreased with additional HPV vaccine doses from 2.17 cases/1000 person-years. The genital warts cases rate was lowest in three-doses group which were 1.5 cases per 1000 person-years which was more statistically significant compared with one-dose. Meanwhile for two-doses and one-dose were 1.76 cases per 1000 person-years and 1.90 cases per 1000 person-years, respectively. The difference between three-doses and two-doses was not statistically significant. The authors analysed the data with Poisson regression analyses indicated that unvaccinated girls had nearly double the risk of genital warts compared with girls who completed the series (IRR 1.90 [95% CI 1.66, 2.18]). Those girls who received one-dose had fewer genital warts than unvaccinated girls, but more than girls who completed the series (IRR 1.22 [95% CI 1.05, 1.41]). The authors also reported that the incidence rates of genital warts were similar in girls who completed 2-two-doses at intervals of either less than five months or five months and above.[18, Level II-1]

5.1.4 Others

The SR by Markowitz et. al. reported that for cervical cytological histological abnormalities, the overall findings showed that out of 1-, 2-, and 3- doses versus unvaccinated; 3-doses of 4vHPV significantly prevent cytological and histological abnormalities compared with unvaccinated.[6, Level II-2]

In a multi-site cohort study by Widdice LE et. al., the authors also investigated the effects of HPV vaccine in concomitant vaccinations with influenza vaccine, hepatitis vaccine, meningococcal vaccine and DTP (diphtheria, tetanus and acellular pertussis) vaccine. The study showed that GMTs level of groups that received other vaccines either in dose 2 or dose 3 HPV vaccine were similar to non-concomitant groups.[17, Level II-1]

Pasmans H et. al. also reported that other than response on HPV-specific IgG, the HPV-Specific-IgA response was also significantly lower for HPV16 and HPV18 in the one-dose group compared to the two-doses and three-doses group. On the other hand, for non-vaccine-types HPV31, 33 and 45, the HPV-Specific-IgA response was lower in one-dose group than the three-doses group only. Meanwhile, for HPV52 and HPV58, there was no difference between the groups. The study also showed that after five years of HPV vaccination, the IgG-avidity index for HPV16 did not differ between different doses whereas for HPV18 the IgG-avidity index was higher in one-dose group compared with two- or three-doses group. The authors also assessed the effects of different doses of 2vHPV vaccine on cellular responses. The observation showed that the levels of HPV-specific-memory B-cells and IFN-γ cells production, Th1 and Th2-cytokines increased as the dose of 2vHPV vaccine was increased.[15, Level II-1]

5.2 SAFETY

The Cochrane review by Bergman H et. al. reported the ADRs upon HPV vaccination. In general, the safety for each group were similar. Those common ADRs were pain in the injection side, swelling and redness. The pain was little to no difference when compared between two doses with three doses either in Group 1 (RR 0.96, 95% CI 0.91, 1.03) or in Group 2 (RR 1.02, 95% CI 0.98, 1.06). Meanwhile for swelling, in Group 1 participants with two doses had less swelling compared with three doses participants for up to seven days follow-up; RR 0.76, 95% CI 0.65, 0.89. The reduction was also seen in redness of two doses participants compared to three doses; RR 0.85, 95% CI 0.75, 0.96. However, in Group 2, there was little to no significant difference between doses for swelling and redness adverse effects; RR 1.01, 95% CI 0.87, 1.18 and RR 1.01, 95% CI 0.87, 1.18, respectively. [1, Level 1]

The RCT by Gilca V et. al. reported that in post-1st dose vaccination, the local ADR and systemic ADR was more frequent in 2vHPV vaccine than 9vHPV vaccine; 87.1% vs. 67.4%; $P < 0.001$ and 66.7% vs. 49.8%; $P = 0.006$, respectively. There was no significant difference in post-2nd dose vaccination. There was also no statistically significant difference was observed in the safety profile of 9vHPV when given in standard (9vHPV + 9vHPV) or mixed schedule (9vHPV + 2vHPV or 2vHPV + 9vHPV). [8, Level II-1]

Neuzil KM et. al. also evaluated any ADRs in all 903 girls who received at least one dose of HPV vaccine. Eight girls experienced weakness, nausea, sweating, pale skin and vomiting within 30 minutes of injection. There were comparable ADRs in all groups either for solicited ADRs (fever, pain at injection-site, itching, redness and swelling) or unsolicited ADRs. No serious ADRs occurred within 30 days of vaccination.[9, Level 1]

The non-RCT by Lazcano-Ponce et.al. showed that the proportion of participants who reported solicited ADR following any vaccination dose was lowest in the adult women group.

On the other hand, pain at the injection site was the most common local symptom in all groups.[10, Level II-1]

5.3 ORGANISATIONAL ISSUES

Stanley M. in in her review raised an issue of constraint in HPV vaccine supply which might affect many countries in maintaining or reaching vaccination coverage especially in low-income countries (LIC) as well as low-middle income countries (LMIC). Because of that, dose reduction could be one of the alternatives for those countries.[19]

Widdice LE et. al. conducted a cross-sectional study among caregiver and HPV vaccinated adolescent to determine factors associated with delayed completion of the three-dose HPV vaccination series in US. Different set of questionnaires were distributed to the caregivers as well as to the vaccinees. The study showed that, caregiver's race and educational level, accessibility of immunization appointments, and adolescent's insurance type were found to be related to delays in completion of 4vHPV vaccine. However, caregiver or adolescent attitudes and belief about on-schedule HPV vaccination or HPV vaccine safety were not.[20]

5.4 ECONOMIC IMPLICATION

Burger EA et. al. conducted an economic evaluation on the long-term health and economic impacts of routine one-dose HPV vaccination compared to no vaccination and two doses HPV vaccination in a low-income country. The authors used three-tiered hybrid modelling approach to capture important behavioral, epidemiological and demographic information. The three models were Harvard-HPV model, Harvard-CC model and Harvard-Scale Up. The authors linked the dynamic agent-based model of HPV transmission (Harvard-HPV) to a static individual-based model of cervical carcinogenesis (Harvard-CC) to capture both direct and indirect 'herd immunity' benefits of HPV vaccination. Then they used a companion population-based model (Harvard-Scale Up) project health and economic consequences for population of Ugandan Women over time. The authors also simulated two scenarios which were Scenario A; comparing routine one dose HPV vaccination of nine-year-old girls starting in 2017 to no vaccination and Scenario B; comparing routine one-dose HPV vaccination to two doses HPV vaccination of nine-year-old-girls. In Scenario A, the number of cervical cancer cases averted with routine one dose HPV vaccination (assumed 80% efficacy and 70% coverage) was projected to increase over time and was greater at longer duration of protection associated with a one dose schedule. When included herd immunity benefits to unvaccinated cohorts of men and women, there was a considerable time delay between initiation of routine 9-year-old HPV vaccination and impact on cervical cancer cases averted at the population level. In contrast, two doses of HPV vaccination assumed 100% lifelong efficacy was projected to prevent 21% of cervical cancer cases in 2,055 compared with no

vaccination. Compared with routine 1-dose HPV vaccination, two doses vaccination with higher efficacy was projected to result in approximately 150,000–310,000 more DALYs prevented (i.e. 5–9% more DALYs prevented compared with one dose) over the lifetime of the analytic cohorts, depending on assumptions regarding the duration of the one dose vaccine protection. Compared with no vaccination, the total disease-specific costs were lower under all vaccination programs in Scenarios A and B due to prevented cancer cases, which accrued/increased over time. The routine two doses HPV vaccination required twice the initial investment of one dose vaccination, while the cost offsets due to cancer prevention was only slightly higher (an additional 5–10%). In addition to that, routine one dose HPV vaccination of 9-years-old girls provided greater health benefit for less money compared with no vaccination regardless of declining scenario. In contrast while two doses vaccination was always more effective than one dose vaccination, the incremental cost of two doses versus one dose depended on the duration of one dose protection. However, when one dose decreasing, the protection was assumed to begin earlier at 10 years, two doses vaccination was less costly and more beneficial compared to one dose vaccination. In sensitivity analysis, higher vaccination coverage with the less efficacious one dose vaccination achieved near-equivalent (i.e., 99%) health benefits in terms of DALYs averted relative to two-dose vaccination, if one dose vaccine protection did not wane. With this assumption, one dose vaccination was cost-saving and two dose vaccinations exceeded the Ugandan per capita GDP threshold. Although the one dose vaccination with higher coverage remained cost-saving regardless of waning assumption, two doses vaccination was considered 'very cost-effective' when one dose protection declines at 10 to 15 years.[21]

5.5 LIMITATIONS

Authors acknowledge some limitations in the review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited the study numbers. Most of studies followed or recruited participants from available cohort of previous HPV vaccination trials. On the other hand, for certain dose especially one-dose HPV vaccination, the included studies recruited the participants from the main cohort who have not completed the exact dosing schedule.

6.0 CONCLUSION

Since three-dose or two-dose HPV vaccination have been approved by the WHO and was widely practiced, single dose HPV vaccination become another option. Based on this Technology Review, several HPV vaccination trials assessed the opportunity of single-dose HPV vaccine among young-girls at age of nine to 14 years-old. The studies found that, the

overall efficacy of single dose HPV vaccine; either with 2vHPV vaccine or 4vHPV vaccine showed significantly lower efficacy when compared with either two-dose or three-dose. Although the GMTs level was significantly lower than other doses, the level was higher than unvaccinated participants. Besides that, single dose of 2vHPV vaccine remained stable for seven years. Comparing one-, two-, and three-dose 4vHPV vaccine with no dose, all dose-schedules showed significant difference in reducing the anogenital warts incidence. No studies were retrieved on single dose 9vHPV vaccination.

The included studies also revealed the efficacy of the different HPV vaccine dosing intervals. Overall, the common range of long interval between first- and second-dose assessed was about seven- to 12-months. Based on that interval, the included studies reported that long interval resulted in higher GMTs level compared to short interval which was commonly defined as three- to six-months interval. One study reported no significant difference in GMTs level and anogenital warts incidence rates with different among interval. One RCT reported that 2-doses schedule in women aged 15 to 25-years old resulted in lower GMCs level than 3-doses schedule but the seropositivity was high in both groups.

In terms of safety, most included studies reported that all HPV vaccine dose schedules at any interval had comparable adverse events. The most common ADRs were pain after HPV vaccine injection, redness at injection site and nausea. No serious ADRs reported.

There was one economic study conducted to evaluate the long-term health and economic impacts of routine one-dose HPV vaccination compared to no vaccination and two doses HPV vaccination in a low-income country. The study reported that, although the one dose vaccination with higher coverage remained cost-saving regardless of waning assumption, two doses vaccination was considered ‘very cost-effective’ when one dose protection declines at 10 to 15 years.

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9.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVID MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 5th February 2021

1 Papillomavirus Infections/
2 Papillomaviridae/
3 Uterine Cervical Neoplasms/
4 HPV.tw.
5 (Human adj1 papillomavirus# infection$).tw
6 (Papillomavirus# adj2 infection$).tw.
7 (HPV adj2 infection$).tw.
8 (Papillomavirus# adj1 infection$).tw.
9 Papillomaviridae.tw.
10 (HPV adj human papillomavirus# virus#).tw.
11 (Human adj1 papilloma virus#).tw.
12 (Virus# adj Human papillomavirus#).tw.
13 (Virus# adj human$ papilloma).tw.
14 (Uterine adj1 cervi# neoplasm$).tw.
15 (Neoplasm$ adj1 uterine cervi#).tw.
16 (Cancer$ adj2 cervi#).tw. (2864)
17 (Cancer$ adj2 uterine cervi#).tw.
18 (Uterine adj1 cervi# cancer$).tw.
19 (Cervi# adj1 neoplasm$).tw.
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 Vaccination/
22 Vaccination$.tw.
23 (Active adj1 immunization$).tw.
24 21 or 22 or 23
25 Dose-Response Relationship, Immunologic/
26 dose.tw.
27 (immunolog# adj1 dos#-respon# relat#).tw.
28 (immunolog# adj1 dos# respon# relat#).tw.
29 (relat# adj1 immunolog# dose-respon#).tw.
30 (relat# adj1 immunolog# dose respon#).tw.
31 26 or 27 or 28 or 29 or 30
32 20 and 24 and 31

33 Immunization Programs/
34 (Aware# adj2 vaccin#).tw.
35 (Program$ adj2 vaccin#).tw.
36 (Campaign$ adj2 vaccin#).tw.
37 (Promot# adj2 vaccin#).tw.
38 33 or 34 or 35 or 36 or 37
39 20 and 38
40 Papillomavirus Vaccines/
41 hpv vaccin# dose.tw.
42 Hpv vaccin#.tw.
43 (Human$ adj1 papilloma virus# vaccin#).tw.
44 (Human$ adj1 papillomavirus# vaccine#).tw.
45 (Papillomavirus# adj1 vaccin#).tw.
46 (Vaccin# adj1 human$ papillomavirus#).tw.
47 40 or 41 or 43 or 44 or 45 or 46
48 20 and 47
49 Immunization Schedule/
50 (Immuni#ation adj1 schedule$).tw.
51 49 or 50
52 24 or 31 or 51
53 47 and 52
54 20 and 53

Other Databases

EBM Reviews - Health Technology Assessment
EBM Reviews - Cochrane database of systematic reviews
EBM Reviews - Cochrane Central Registered of Controlled Trials
EBM Reviews - NHS economic evaluation database

} Same MeSH, keywords, limits used as per MEDLINE search

PubMed
INAHTA
US FDA

} Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized 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)

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