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Intervals of 12 months and 36-96 months are Non-Inferior to 6 months in HPV16/18 Antibody Response: Findings of a Systematic Review and Meta-Analysis of Two-Dose HPV Vaccine Schedules with Intervals of Six Months or Longer

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Abstract

Human Papillomaviruses can cause cancer of multiple human anatomical sites, with essentially all cervical cancer cases worldwide being attributable to persistent HPV infections. HPV vaccination provides effective protection against HPV infections. An estimated 90% of cervical cancer cases occur in low and middle incomes, but only 20% of these countries have implemented HPV vaccination. In contrast, 82% of high income countries have included HPVV in their national vaccination programs. Current HPV vaccination schedules which recommend administering multiple doses within six months can be logistically challenging for both low- and middle-income as well as high-income countries. The ongoing global shortage of HPV vaccines that is expected to last until 2024 is an additional challenge. There are suggestions to extend the two dose 0,6 months schedule for the primary target population (females 9-14 years) to longer intervals, even up to 3-5 years, to ease logistics and relieve demand in the short-term. Interval extension however, requires evidence to support whether it will be beneficial. This paper reports findings of a systematic review of available studies, that compares the immunogenicity, efficacy and effectiveness of two-dose schedules of 7 or more months between doses with schedules of 6 months between doses. We found, similar to a previous systematic review, that increasing the two-dose interval from 6 months to 12 months resulted in non-inferior immunogenicity. Also an increase of the dose-interval from 6 months to 36-96 months, results in non-inferior antibody response to HPV6 and high risk HPV types 16 and 18, but not HPV11, based on data from an observational study. The effect of an interval of 8 or more months compared to an interval of 4-7 months on AGW incidence was inconclusive and no studies were available to assess efficacy or effectiveness against HPV infections or cancers. This highlights the acute scarcity of evidence necessary to evaluate two-dose schedules with intervals longer than 6 months. Nevertheless, our

non-inferiority findings indicate that a schedule with a 12 month interval can be adopted in lieu of one with a 6 month interval. However, even though the 36-96 month interval is indicated to be no worse than a 6 month interval in antibody response to HPV 16 and 18, the low certainty of the estimates derived from it, requires that it be studied further to confirm its effect on immunogenicity.

List of Abbreviations

AGW	Anogenital wart
ATTP	According to protocol population
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	competitive Luminex ImmunoAssay
ELISA	Enzyme Linked Immunosorbent Assay
GMC/T	Geometric mean concentration or titer
GRADE	Grading of Recommendations Assessment Development and Evaluation
HPV	Human Papillomavirus
hrHPV	high risk Human Papillomavirus
HPVV	Human Papillomavirus vaccines
PBNA	Pseudovirion Based Neutralisation Assay
RCT	Randomised control trial
WHO	World Health Organisation

Introduction to the Public Health Problem

The Human Papillomavirus (HPV) is the most common sexually transmitted infection globally[1,2] and the leading viral cause of cancers worldwide[3,4]. HPV is a risk factor for multiple cancers, accounting for an estimated 29.5% of infection-related cancers worldwide[4] and an even greater proportion (54%) of infection-related cancers in Canada[5]. There are over 100 genetic types of HPV, of which 14 are qualified as high-risk HPV (hrHPV) types based on their oncogenic potential. Persistent infection with HPV types 16 and 18 are associated with over 70% of cervical cancer cases, and together with HPV types 31, 33, 45, 52, 58, account for approximately 90% of cancers of the cervix[3]. HPV infections are also associated with non-cervical cancers, including anal, penile, vaginal, vulvar and oropharyngeal cancers[2,3,5]. HPV types 6 and 11 are low-risk HPV types, however they cause over 90% of ano-genital warts (AGWs)[2,6]. Although non-malignant, AGWs can cause discomfort, negative psychosocial effects and substantial direct treatment costs in many populations[7–11].

Women bear a predominant share of the global HPV-related cancer burden, due to cervical cancer having the highest prevalence and mortality of all HPV-related cancers[2,3]. In 2018, all 570,000 new cervical cancer cases worldwide were attributable to HPV infection[3]. HPV-related cancer burden is greatest for women in developing and least developed countries (human development index <0.8) with approximately 88% cervical cancer deaths occurring among women in these countries[12].

HPV vaccines (HPVVs) have delivered significant reductions in HPV infections and associated morbidities in countries that have implemented HPV vaccination programs[13–16]. Meta-analysis of data from fourteen such high-income countries showed that after 5-9 years of HPV vaccination, these countries achieved significant reductions in the prevalence of hrHPV types 16, 18, 31, 33

and 45 among women. Highest reductions between the pre-vaccination and post-vaccination periods in these countries were seen for younger women 13-18 years, with the prevalence of HPV16 and 18 reduced by as much as 83%[14]. Significant reductions in cervical intraepithelial neoplasia grade 2 or higher (CIN2+; a pre-invasive pre-cursor to cervical cancer) and AGWs were also seen. These effects were greatest among women 15-19 years (51% reduction for CIN2+ and 67% reduction of AGWs)[14]. With vaccinated females being protected against HPV infection, males were less likely to be exposed to the virus during female sexual contact. The population level benefits of HPV vaccination among women were therefore extended to males through herd effects. This was observed as significant decreases in AGW diagnoses among men 15-24 years, with estimates of reduction as high as 48% among men 15-19 years[14].

Despite the reduction in HPV disease burdens realized in high income countries, cervical cancer remains a global public health priority. This is due to unacceptably high current and forecasted cervical cancer incidence in lesser resourced nations, particularly the world's poorest[17]. Higher cervical cancers in poorer countries results from inadequate cervical cancer prevention programs for screening and effective treatment of cervical cancer precursor lesions[18,19]. The proven effectiveness of HPV vaccination in reducing HPV infections led to its inclusion as an essential component in the World Health Organization's (WHO) Global Strategy Towards the Elimination of Cervical Cancer as a Public Health Problem. This Global Strategy outlines 2030 country-level targets for primary, secondary and tertiary prevention through vaccination, screening and treatment, respectively. These targets are: 90% of girls being fully vaccinated against HPV by age 15; 70% of women receiving high-precision HPV screening at ages 35 and 45 years; and 90% of women identified with cervical cancer receiving treatment and care. The achievement of these

targets by each country is proposed to enable a reduction in cervical cancer incidence to less than 4 per 100,000 women-years within the twenty-first century[17].

There are, however, challenges to achieving the primary prevention target using HPVVs with multi-dose schedules that require two or sometimes three visits within one year. Such schedules can be challenging for vaccine delivery mechanisms. For example, school-based delivery of two or three doses within six months, as done in provinces across Canada[20] and in many high-income countries, require health-care professionals to make multiple visits to schools within a single school year. Another factor that operates at the global macro level, is socioeconomic disparity that contributes to inequities in access. This is apparent as HPV vaccination has been implemented in 84% of high-income countries but only 31% and 12% of middle and low-income countries, respectively[21]. Further, projections show that current production capacities of HPVVs are well below the volumes required to achieve vaccination coverage required by the WHO's Global Strategy[21,22]. Within countries, expanding vaccination coverage is also impeded by additional contextual social, personal and health system factors[23–26]. Considering the myriad of interacting factors, the Global Strategy promoted by the WHO has also called for research to simplify HPVV schedules and "achieve the same population impact at a lower cost"[21]. One way to achieve this simplification is to increase the interval between doses. For immunocompetent children 9-14 years, the preferred recommended schedule for administering the HPVV is two doses, spaced at an interval of 6 months. Although a six-month interval is favoured, the WHO indicates that with the absence of evidence of the maximum interval between doses where the vaccine remains effective, intervals of 12-15 months are also acceptable[6]. If these two doses could be administered later, even longer than 12-15 months apart, then vaccine doses needed per year could be substantially reduced, at least until supply capacity can meet demand. Further logistical arrangements to deliver the two

doses within 6-15 months could be reduced. Longer intervals would also more readily facilitate co-administration of HPVV with other vaccines required by the primary target group (girls 9-14 years). A recent systematic review using relevant studies available up to September 2018, Bergman et al found that longer intervals for two-dose schedules provided stronger antibody response than shorter intervals. This was based on studies comparing an extension of the two-dose interval from 2 to 6 months, and also from 6 to 12 months[27]. Improved antibody response of a six-months interval relative to a two-months interval between doses for two-dose schedules was already well established in females 9-14 years. It is unclear however, if the trend of increasing antibody response with interval length extends to intervals beyond twelve months. In consideration of the HPVV shortage the WHO Strategic Advisory Group of Experts (SAGE) on Immunization suggested that spacing two doses at intervals of 3-5 years could be considered, but would constitute "off-label" use of the vaccines[28]. A synthesis of evidence from the current body of knowledge, that includes two-dose intervals beyond 12 months could provide timely insights on the potential of such extended-dose schedules to effective. Further, Bergman et al 2020[14] did not examine the effect of extended intervals on cell-based immune responses or HPV-related diseases. This paper therefore extends upon the work of Bergman et al 2020, by comparing the effect of using dosing intervals beyond seven months on humoral and cellular immunogenicity, as well as effectiveness of HPVVs. This will provide additional insights relevant to optimizing HPVV schedules.

Purpose of the Paper

Vaccination is a highly effective strategy for primary prevention of HPV infection, cervical cancer precursors and other HPV-related diseases. Despite the demonstrated effectiveness of HPVVs, their population-level impact has not been maximized[29], largely due to limited access in lower income countries resulting from financial constraints, as well as suboptimal vaccine coverage and compliance with multi-dose vaccine schedules globally[30,31]. Optimizing vaccination schedules is necessary for the success of vaccination programs and the elimination of cervical cancer. The number of vaccine doses and their spacing are critical features of the vaccination schedule. Simplifying vaccine schedules by reducing the number of doses or allowing for more flexible spacing of follow-up doses could improve population vaccine coverage, completion of vaccine series and may improve the cost-effectiveness of vaccination programs[32,33]. An increase in the spacing of the two doses could be more convenient for administration of the vaccine to patients, and probably allow more efficient integration of the HPVVs with other routinely-administered vaccines. Recent shortfalls in the supply of all three HPVVs[34] threaten to constrain the WHO's Global Strategy Towards the Elimination of Cervical Cancer as a Public Health Problem, which aims to expand vaccine coverage and protection against HPV. Allowing extended intervals for HPV vaccination would ease administration for public health. In addition, with the current global shortage in HPVV supplies, longer intervals between doses could reduce the shortfall between supply and demand by delaying the second dose until supply increases. Evidence of the immunogenicity and effectiveness of HPVVs when the two doses are spaced at longer time intervals could therefore inform possible flexibility regarding existing HPVV schedules.

Review Question

Do intervals longer than 6 months affect the immunogenicity, efficacy/effectiveness of HPVVs administered in a two-dose schedule to children aged 9-14 years and young adults 15-26 years compared to a six month interval?

Objectives

1) To determine whether HPVV schedules of 0, 6 months (+/- 1 month) and 0, 7+ months are non-inferior in the level of antibody response and seroconversion rates for children aged 9-14 years and young adults 15-26 years.

2) To determine whether HPVV schedules of 0, 6 months (+/- 1 month) and 0, 7+ months are non-inferior in cellular immune response for children aged 9-14 years and young adults 15-26 years.

3) To determine whether HPVV schedules of 0, 6 months (+/- 1 month) and 0, 7+ months are non-inferior in their efficacy in protecting against HPV infections and HPV-related diseases for children aged 9-14 years and young adults 15-26 years.

4) To determine whether HPVV schedules of 0, 6 months (+/- 1 month) and 0, 7+ months are non-inferior in their effectiveness in protecting against HPV infections and HPV-related diseases for children aged 9-14 years and young adults 15-26 years.

Critical Review of Relevant Literature

HPV Vaccines and Basis of Protection (Immune Response)

HPVVs are recombinant subunit vaccines containing the major capsid L1 protein of vaccine strains. Three HPVVs are currently licensed for use. The bivalent vaccine was licensed in 2007 and targets HPV types 16 and 18. The quadrivalent vaccine was licensed a year earlier and targets HPV types 6 and 11 in addition to HPV types 16 and 18. The nonavalent vaccine was licensed in 2014 and protects against HPV types 31, 33, 45, 52 and 58, in addition to the four types that the quadrivalent vaccine protects against[6].

HPVVs are prophylactic and provide greatest protection when individuals are vaccinated prior to HPV exposure, usually, before sexual debut[35,36]. HPVVs trigger the adaptive immune system to produce elevated levels of antibodies, B-cells and T-cells that target HPV antigens for neutralization and destruction[37–40]. A study of cervical secretion samples after intramuscular vaccination showed that there is exudation of serum antibodies to the mucosa to bolster protection against natural HPV infection[41,42]. This protection is durable over the long term due to long-lasting antibody producing B-cells and memory B-cells[43–45]. It is proposed that long-lasting plasma B-cells contribute to the sustained persistence of antibody protection[43]. Memory B-cells direct the proliferation and rapid production of antibody producing B-cells if HPV challenge occurs subsequently, this is known as the anamnestic response[43–45]. Helper T-cells are proposed to play an accessory role in supporting the development and maintenance of an effective antibody response[41,46]. Since HPVVs contain a component of the viral capsid, they stimulate antibodies that neutralize the HPV particle to prevent establishment of infection. The vigorous antibody response induced by the HPVVs is therefore highly protective when vaccines are administered prior to infection[47,48]. The minimal anti-HPV antibody threshold required for effective protection against

HPV infections and HPV associated diseases is unknown[36,42,49]. During the peak antibody response to HPVV, neutralizing antibody levels are as much as 100 times above that of natural HPV infection[50,51]. Natural HPV infection, even with its much-reduced antibody elicitation, also generates protective antibody levels in a subset of infected individuals[52], albeit insufficient to fully protect against subsequent reinfection[53]. It is known however, that antibody levels generated by HPVVs in young women, 15-26 years old, on a three-dose schedule shows efficacy in preventing HPV infection and associated genital diseases including CIN2+ up to five years post-vaccination[47,48]. Consequently, it was recommended that evaluation of different schedules of HPVVs in girls 9-14 years, is by assessing non-inferiority of their antibody response to the antibody response among women 15-26 years, assuming that with comparable immunogenicity also efficacy would be comparable. In 15-26 year old women, efficacy against clinical outcomes after three-dose schedule is established[39,51]. This principle is called immunobridging.

Evolution of HPV Vaccine Schedules

All three HPVVs were originally approved for administration on a three-dose schedule[54]. The first two prime doses were administered 1-2 months apart, followed by a boosting dose after a longer interval. This schedule was guided by the Hepatitis B vaccine which is also a recombinant vaccine[44]. Such a schedule was thought to be necessary to generate long-lasting antibody and cellular memory response to recombinant subunit vaccines[51]. Multiple studies have since showed that alternate schedules where the dose intervals were extended or the number of doses reduced are as immunogenic as three-doses, and therefore comparable protection is assumed[44,46,51,55,56].

Using the immunobridging comparison, it was found that two doses provide acceptable protection for females under 15 years of age[35,57,58]. With these insights, the WHO revised the recommended HPV immunization schedule for immunocompetent adolescents under 15 years to two doses to be

administered at an interval of 6 months between doses (0, 6 months) for the quadrivalent vaccine and an interval of 5-13 months between doses (0, 5-13 months) for the bivalent and nonavalent vaccines[1,6,59]. The three-dose schedule for individuals 15 years and over were maintained[1,6,59], but there have been recent suggestions that the two-dose recommendation should be extended to individuals up to age 18[60,61].

Studies utilising data from delayed or incomplete HPVV series revealed preliminary insights into the effectiveness of alternate schedules. LaMontagne et al [62] proposed that the vaccine schedule impacts the timing of the peak antibody response. In their study of alternate three-dose schedules, LaMontagne et al found that a schedule administered at 0, 12, 24 months was inferior with regard to antibody levels to the standard schedule administered at 0, 2, 6 months at 1 month post-last-dose, but non-inferior at 32 months post-last-dose[62]. Although the 0, 12, 24 months schedule produced antibody levels at 1 month post-last-dose that were lower compared to the standard schedule, it is not known whether this translates to lower protection during this period, since the minimal immune correlates of protection against HPV infection have not been established[51,63]. Another alternate schedule that shows promise is administering two doses with intervals beyond one year[64,65]. Together, the insights into the immunogenicity of alternate schedules of HPVVs suggest that more flexibility regarding the recommended intervals of HPV vaccination schedule may be possible. With a two-dose schedule of 0, 6 months being the standard commonly applied for children 9-14 years, assessment of the effect of extending the interval beyond 6 months could delineate an ideal maximum time interval for administering the second dose. Insights of potentially efficacious extended intervals are especially valuable in guiding decision making to maximise public health benefits.

Vaccine Schedule as a Moderator of Immune Response

The timing of the administration of HPVV doses in relation to each other as well as the age administered can moderate the levels of anti-HPV antibodies produced post-vaccination. A study of three-dose schedules with different intervals found that delayed administration of the second dose resulted in increased antibody titers relative to when the second dose was administered on-time, according to the 0, 2, 6 month schedule[66]. This study also found that antibody levels produced from delayed administration of the third dose were non-inferior to that of on-time administration of the third dose. Also, antibody levels generated by a 0, 1 month or 0, 2 month schedule of the bivalent HPVV were inferior to that generated when the vaccine was administered on a 0, 6 month, two-dose schedule[66,67]. Timing also impacts the effectiveness of the quadrivalent HPVV against condyloma. Compared to the standard three-dose schedule (0, 2 6 months), two doses given 4-7 months apart had similar effectiveness against condyloma, whilst two doses given 0-3 months apart had reduced effectiveness[68]. These indications that the timing of HPVV doses impacts both levels of HPV antibodies and protection against condyloma, warrants exploration of optimal timing for the second dose of the HPVV in a two-dose schedule. Understanding optimal timing of the second dose could guide refinements of HPV vaccination programs globally to improve vaccine delivery and ultimately population protection.

Systematic Reviews and Meta-analyses

The recognition of systematic reviews as a formal type of research with recognizable value for evidence synthesis occurred in the 1970s[69]. Standardized methodologies and tools have been developed for executing systematic reviews[70,71]. These standards aim to ensure that the products of the substantial efforts required to execute a systematic review generate high quality, organized, appraised and integrated evidence of minimal bias. Such evidence is significant for decision

making in health and social contexts to enhance accountability[72]. Systematic reviews may include a meta-analysis as a quantitative synthesis of the accumulated evidence on the topic. The term meta-analysis was coined in 1976 by Gene Glass and methods for appropriate integration and statistical analyses of data from multiple studies have also subsequently been developed[73]. This analysis will apply relevant standards, methodologies and tools, developed for systematic reviews and meta-analyses, to explore the defined research question.

Methods

A protocol was developed for the execution of this systematic review and registered with the International Prospective Register of Systematic Review (PROSPERO), under protocol number: CRD42019141959. Reporting of the review was done according to with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Literature search and study selection

Briefly, a population, intervention, comparator and outcome (PICO) search strategy was developed and used to conduct a systematic search for relevant studies in peer-reviewed and grey-literature databases. The databases: MEDLINE (Ovid), EMBASE (Ovid), Cochrane Central Register of Clinical Trials, PUBMED and CINAHL were searched using this PICO search strategy (Appendix 1), which was adapted to each database based on their syntax and thesaurus. The search term "HPV Vaccine" was used to search ClinicalTrials.gov, GSK study register, MERCK clinical trials, International Clinical Trials Registry Platform, EU Clinical Trials Register and Drugs@FDA for grey literature. Two review team members, ACF and RD, screened references for suitability based on pre-defined inclusion criteria. Inclusion criteria were:

1. study participants received first HPVV dose between age 9-26 years inclusive,
2. administration of any combination of bivalent, quadrivalent or nonavalent HPVVs in a two-dose schedule to females and/or males and
3. presentation of data on immunogenicity, effectiveness or efficacy of two doses of HPVV administered 0,6 months (+/- 1 month) as well as two doses administered 0,7+ months.

Studies were excluded if:

1. any other agent was administered simultaneously with HPVV for treatment of or protection against HPV related outcomes,
2. only populations with specific diseases were included,
3. the second dose of HPVV was administered earlier than five months after the first dose,
4. the vaccine formulation administered is different from the licensed vaccine formulation, or
5. the study is reported in a language other than English.

Data Extraction and Analyses

Data were independently extracted from included studies by ACF and RD onto prepared data extraction worksheets and both sets of extracted data checked for agreement and accuracy by ACF. Bias in each study was assessed using the Cochrane Risk of Bias v2 for clinical studies[74] and the Cochrane Risk of Bias in Non-Randomised Studies of Intervention (ROBINS-I)[75] tool for observational studies. The quality of the evidence available to assess each study objective was then assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach[76].

Outcome measures reported for immunogenicity and effectiveness indicators were used to derive a relative measure for comparing schedules of 0, 7+ months (0, 7+m) to the reference schedule of 0, 6 months (0,6m). To validly compare effects across studies, within-study relative measures for the effect of 0,7+m versus 0,6m intervals on immunogenicity outcomes were first generated to obtain an effect measure that controls for inter-study methodological variations such as antibody assays[77]. Using Revman 5.2, relative measures were then pooled across studies with identical study design and low to moderate heterogeneity, I^2 <50%, to provide a pooled estimate of effect. Non-

inferiority (NI) was then assessed using specified NI margins for the pooled estimates (Table 1). These NI margins were adopted from previous non-inferiority studies related to HPVVs and their use will facilitate comparison of our findings to previous studies [78,79]. Where NI was demonstrated, superiority was assessed, as pre-specified in the protocol for this review. Superiority is demonstrated when the lower limit of the 95% CI of the estimate exceeds 1 for ratios and 0 for differences in proportions or rates.

Table 1: Non-Inferiority Margins Used in Comparing 0, 7+m vs 0,6m Schedules

Outcome	Measures	Non-Inferiority Margins for 0,7+m vs 0,6m Lower limit of 95% confidence interval is:
Immunogenicity		
Antibody Levels	GMC/T	> 0.5 for ratio
Cell based Immunity	HPV type specific B or T-cells per million B or T-cells	> 0.5 for ratio
Seroconversion	Proportion	> -10% for difference
Effectiveness		
HPV Infection	Proportion Rate	> -10% for difference ≥ 0 for rate difference
Rates of Any HPV Related Disease	Rate	≥ 0 for rate difference

GMC/T= Geometric mean concentration or titer.

Results

Description of Included Studies

Of the 1276 records screened for eligibility, 11 were selected for inclusion in this systematic review (Figure 1) and these represented four unique studies. Each is described below and a summary of included publications provided in Table 2.

Figure1: PRISMA Flow chart describing the study selection process.

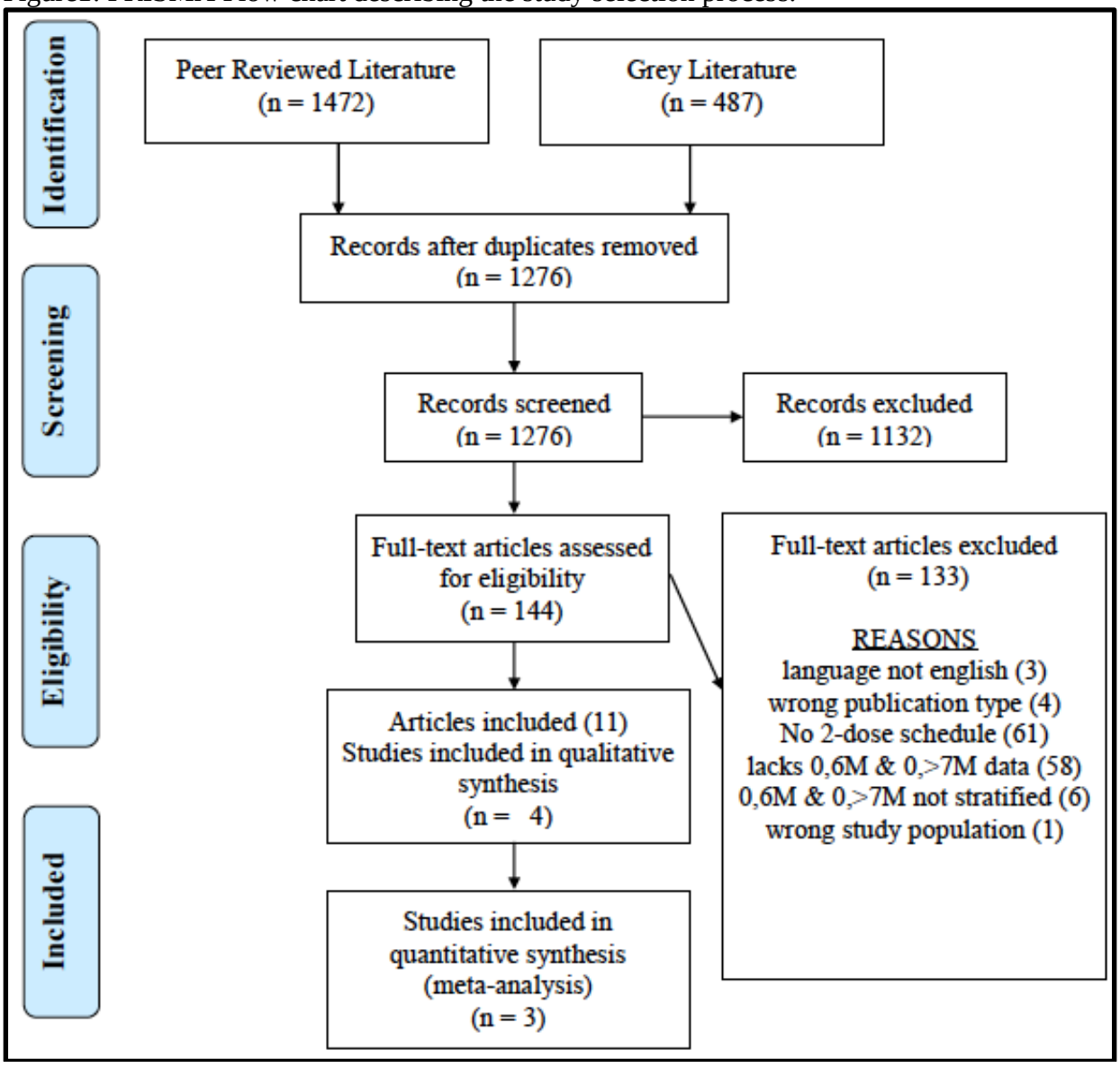


Table 2: Summary of the characteristics of included studies

Unique Studies	Study/Trial ID	Study Participants (sex, age in years)	Intervention (Vaccine & Schedule)	Sample Size (Total Vaccinated, n)	Publication (Author_Year)	Outcomes Reported																			
						Immunogenicity (Time post dose 1/months)																		Efficacy/ Effectiveness	
						Seroconversion						GMC/T						Cellular Immunogenicity							
						7	13	18	24	36	36-96	7	13	18	24	36	36-96	7	13	18	24	36	36-96	AGW	Incident: HPV/ Cancer/ Pre-cancer
1	NCT01381575 & EUCTR2011-000757-22-IT	F, 9-14 F, 9-14	2v @ 0,6m 2v @ 0,12m	550 415 965	GSK 2011* Huang etal 2017 Puthanakit et al 2016	●	●	●	●	●	○	●	●	●	●	●	○	●	●	●	●	●	○	○	○
						●	●	●	●	●	○	●	●	●	●	●	○	●	●	●	●	●	○	○	○
						●	●	○	○	○	○	●	●	○	○	○	○	●	●	○	○	○	○	○	○
2	NCT01984697	F, 9-14 M, 9-14 FM, 9-14	9v @ 0,6m 9v @ 0,6m 9v @ 0,12m	301 301 301 903	Merck 2013* Iversen etal 2016 Joohee etal 2016 Yan etal 2016	●	●	○	●	●	○	●	●	○	●	●	○	○	○	○	○	○	○	○	○
						●	●	○	●	●	○	●	●	○	●	●	○	○	○	○	○	○	○	○	○
						●	●	○	○	○	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○
						●	●	○	○	○	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○
3	NCT0256795 & NCT03431246	FM, 9-14 F, 9-14	9v @ 0,6m 4v/9v @ 36-96m	173 31 204	Gilca etal 2019	●	○	○	○	○	●	●	○	○	○	○	●	○	○	○	○	○	○	○	○
4	Lamb etal 2017	F, ≤16 F, 17-19	4v @ 4-7m 4v @ 8+m 4v @ 4-7m 4v @ 8+m	8095 1894 9989 2965 615 3580	Lamb etal 2017	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○

●= available data, ○= no data, 2v= bivalent HPV vaccine, F= female, M= make, FM= female and male, 4v= quadrivalent HPV vaccine, 9v= nonavalent HPV vaccine, 4v/9v= mixed regimen of 4v then 9v HPV vaccine, GMC/T= geometric mean concentration/titres from enzyme linked immunosorbent assay, competitive luminex immunoassay or pseudoviron based neutralization assay, AGW= ano-genital warts, *= source from which data were extracted when multiple publications available

GSK_NCT01381575 (Bivalent study)

Study NCT0131575 is a GlaxoSmithKline (GSK) sponsored study, conducted from June 29, 2011 to June 28, 2014. It is a RCT that evaluated the immunogenicity and safety of GSK's HPV16/18 vaccine (Cervarix®) when administered according to alternative 2-dose schedules of 0,6 months and 0,12 months in females 9-14 years compared to the standard 3-dose schedule (0,1,6 months) in 15-25 year old females. Primary study outcomes measured were number of anti-HPV16/18 seroconverted participants at one month after the last vaccine dose, as well as anti-HPV 16 and anti-HPV-18 antibody concentrations, measured by Enzyme Linked Immunosorbent Assay (ELISA) at one month after the last vaccine dose. Secondary outcomes related to immunogenicity were:

1. seroconversion for anti-HPV16/18 after dose 1 at day 0, then at months 7, 12, 18, 24 and 36 for participants receiving vaccine at 0,6 months and 0,1,6 months, and at day 0, months 13, 18, 24 and 36 for participants receiving vaccine at 0,12 months;
2. anti-HPV16/18 measured by ELISA after dose 1 at day 0, then at months 7, 12, 18, 24 and 36 for participants receiving vaccine at 0,6 months and 0,1,6 months, but at day 0, months 13, 18, 24 and 36, for participants receiving vaccine 0,12 months;
3. anti-HPV16/18 neutralising antibody measured by PBNA for a subset of participants after dose 1 at day 0, then at months 7, 12, 18, 24 and 36 for participants receiving vaccine 0,6 months and 0,1,6 months and at day 0, then months 13, 18, 24 and 36 for participants receiving vaccine at 0,12 months;
4. Anti-HPV 16/18 specific T-cell after dose 1 at day 0, then at months 7, 12, 24 and 36 for participants receiving vaccine at 0,6 months and 0,1,6 months and at day 0, then months 13, 18 and 36 for participants receiving vaccine at 0,12 months;

5. Anti-HPV16/18 specific memory B-cells after dose 1 at day 0, then months 7, 12, 24 and 36 for participants receiving vaccine at 0,6 months and 0,1,6 months and at day 0, then months 13, 18 and 36 for participants receiving vaccine at 0,12 months.

Data from this study was reported by four publications identified by our search strategy (Table 2). This study will be subsequently referred to as the bivalent study[80].

Merck_NCT01984697 (Nonavalent study)

This study was sponsored by Merck Sharp & Dohme Corporation. It is a RCT that investigated the safety and immunogenicity of nonavalent HPVV when administered in alternate two-dose schedules of 0,6 months and 0,12 months in boys and girls 9-14 years, compared to women 16 to 26 years who received standard three-dose regimen at 0, 2, 6 months. The primary study outcomes were antibodies to vaccine HPV types (HPV6, 11, 16, 18, 31, 33, 45, 52 and 58) at 1 month after the last dose of planned regimen, as measured by competitive Luminex Imunoassay (cLIA). Secondary outcomes were:

1. seroconversion to HPVV types at 1 month after last dose of the planned regimen;
2. persistence of vaccine type antibodies, measured by cLIA at months 24 and 36 after the first dose;
3. persistence of vaccine type antibodies, as measured by percentage seroconverted participants to vaccine type HPV at months 24 and 36 after first dose.

Data from this study was reported by five of the publications identified by our search strategy (Table 2). This study will be subsequently referred to as the nonavalent study[81].

Gilca et al 2019

This non-randomised study was a post hoc analysis comparing anti-HPV6, 11, 16 and 18 antibody response measured by ELISA, of 173 males and females aged 9-10 years who received two-doses of nonavalent vaccine at 0, 6 months (6m), to 31 girls aged 9-14 years who received quadrivalent vaccine as a first dose and nonavalent vaccine as a second dose 3-8 years later. The 0, 6m participants were the comparator group for a separate RCT (NCT02567955), and was adopted as the comparator group for this post hoc analysis. Participants in the intervention group that received vaccine at 0, 36-96 months (36-96m) were identified in a school-based vaccination database as non-compliant cases who completed only one dose of the recommended two-dose vaccine schedule. This study will be subsequently referred to as Gilca et al[64].

Lamb et al 2017

This is a cohort study, that assessed the incidence of condyloma in Swedish women initiating HPVV between 2006 and 2012, and who received two doses of the quadrivalent vaccine at varying intervals between doses, including intervals of 4-7 months (4-7m) and 8 or more (8+m). National registries were linked to provide the study exposure and associated outcome data. This study will be subsequently referred to as Lamb et al[68].

Risk of Bias Analysis

The two randomised studies had an overall low risk of bias (Figure 2), when judged using the RoB2 tool. The only area that not ideal was the lack of blinding in regard to participants'

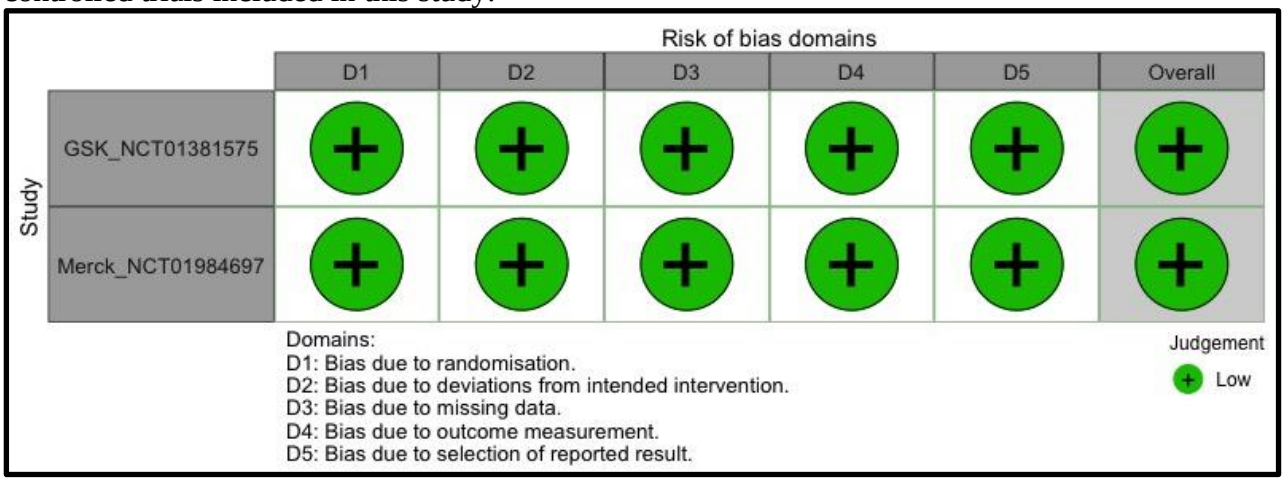
assigned study group, ie. receiving vaccine at 0, 12 months (12m) versus 0, 6 months (6m), in both studies. The effect of lack of blinding in these studies where biomarkers such as antibody levels and cell frequencies are the outcomes assessed, is anticipated to be low.

The observational studies by Gilca et al and Lamb et al were assessed using the ROBINS-I tool. Gilca et al 2019 was assessed to have an overall moderate risk of bias (Figure 3). Confounding by indication and volunteer bias could potentially be operating in this study. Confounding by indication could arise since participants in the 36m group were all non-compliant vaccinees. Social deprivation was associated with lower vaccination coverage in Quebec[82] (the province where this study was done), and in Ontario lower income was associated with incomplete vaccine series[83]. The antibody response is generally robust to sociodemographic factors such as race and region of residence[84], however we cannot completely exclude the chance that sociodemographic factors associated with vaccine non-compliance could distort the true effect of a 36-96m interval GMT. Additionally, higher vaccine-type antibody titres have been observed or girls who were seropositive for HPV prior to HPVV than for girls seronegative at baseline[48,84]. The 36-96m of vaccine non-compliance provides substantially greater opportunity for higher HPV exposure, which could potentially inflate the peak GMT observed after the second vaccine dose, again distorting the true effect of the 36-96m interval. No information on the sexual risks of the comparator and intervention groups were reported. There is also a potential for volunteer bias in this study since only non-compliant vaccinees who consented to receiving the second dose could be included. The authors however, did not report the proportion of the eligible population that consented or how representative they are. This publication completed the peer-review process without the aforementioned information being included. It may be an indication that the authors and reviewers did not consider that information to be highly influential on the

outcome of antibody concentration. Although the missing information would have supported firm establishment of the quality of the evidence from this study, the extent to which they would bias a robust, objective biomarker like antibody levels is not definitively clear. Consequently a more severe risk of bias rating than moderate was not assigned.

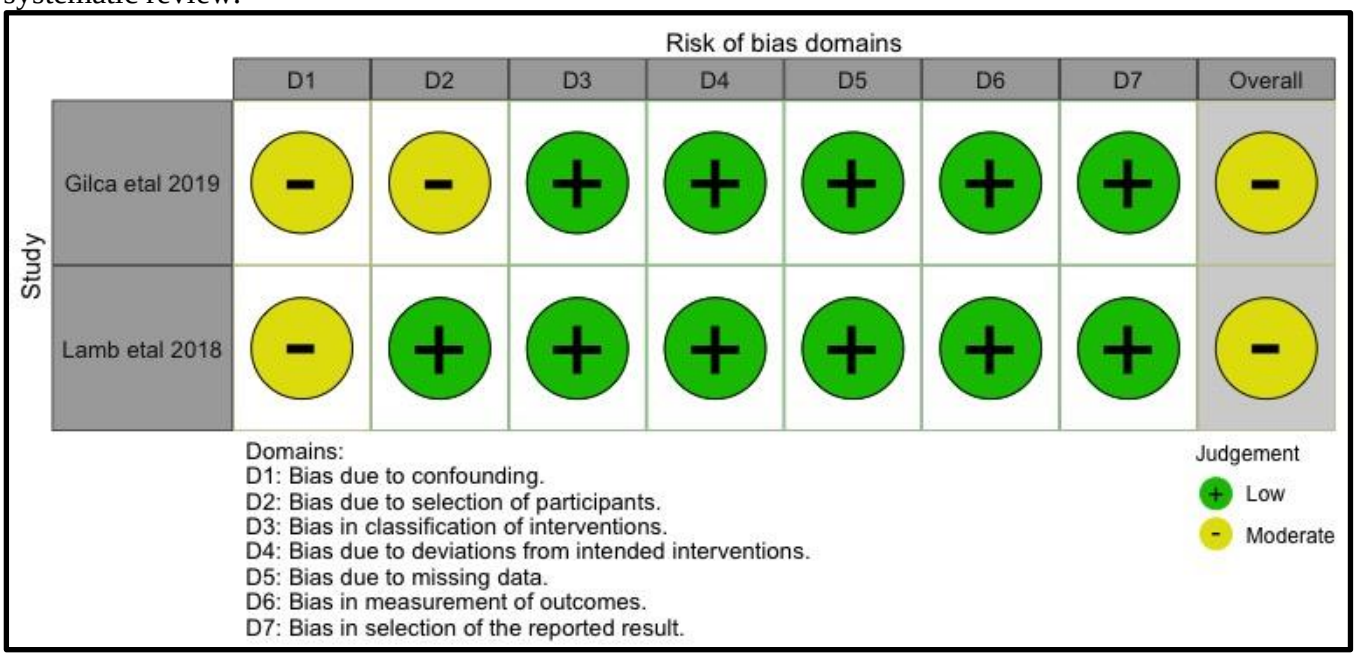
Lamb et al was assessed to have moderate risk of bias due to residual confounding[68]. The results of the risk of bias for the randomised and non-randomised studies are presented in Figures 1-2. Detailed risk of bias assessments are provided in Appendix 2.

Figure 2: Traffic light plot summarizing the risk of bias assessment of the two randomised controlled trials included in this study.



The assessment was conducted using the RoB2 tool and visualized using robvis.

Figure 3: Traffic light plot of risk of bias assessment of non-randomised studies included in this systematic review.



The assessment was conducted using the ROBINS-I tool and visualized using robvis.

Synthesis of Outcomes

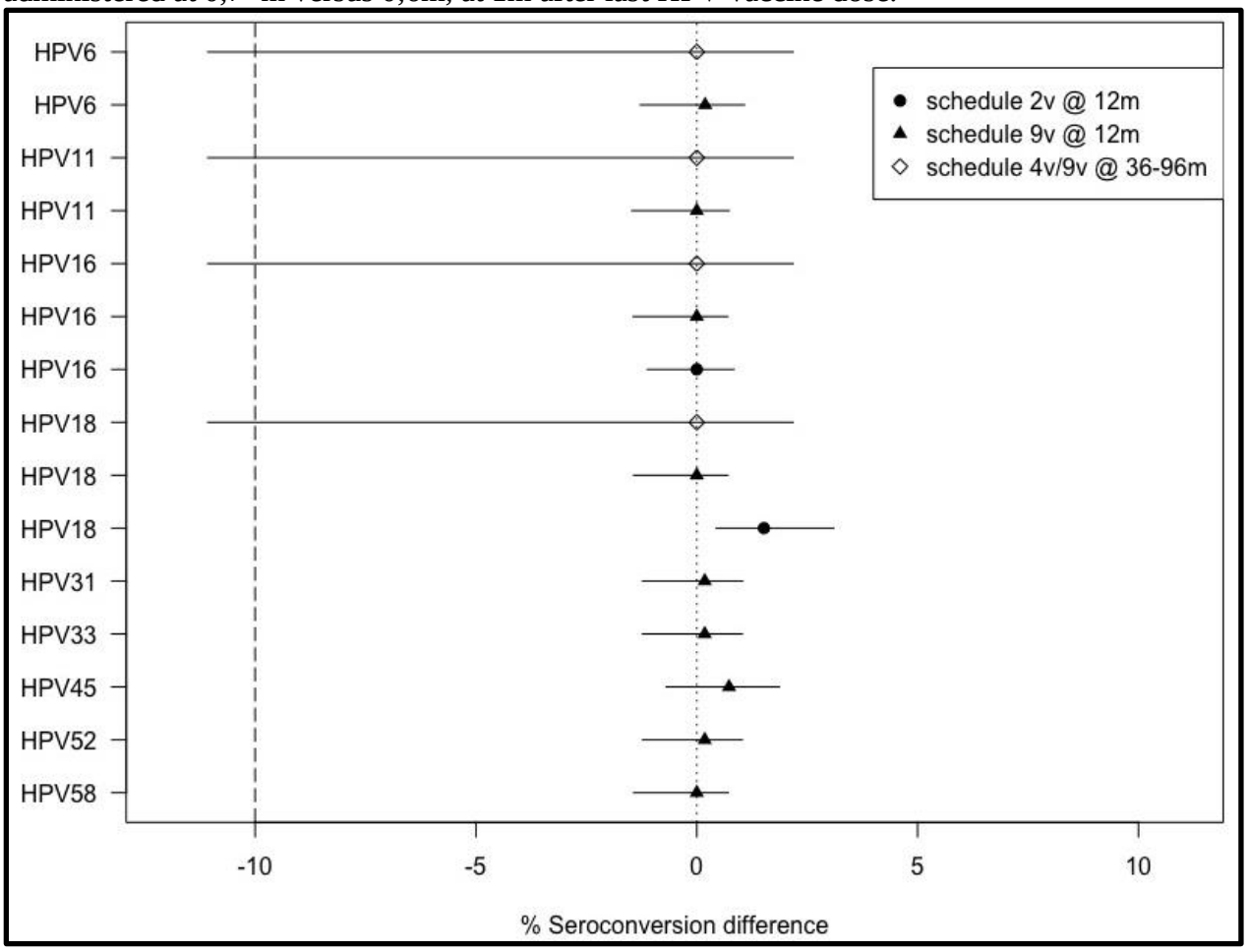
Immunogenicity

Three studies examined the effect of two-dose schedules with time intervals of 6m compared to 7+m between two doses, on HPVV immunogenicity. Two of these studies, the bivalent and the nonavalent studies examined 0, 12m and 0, 6m two-dose schedules. The third study, Gilca et al, compared a 0, 6m dose interval to a 36-96m dose interval. The effects of the 7+m interval is therefore reported in terms of 0, 12m and 0, 36-96m. Immunogenicity was reported in terms of seroconversion rates, humoral antibody response, and cellular immune responses.

Seroconversion and Seropositivity

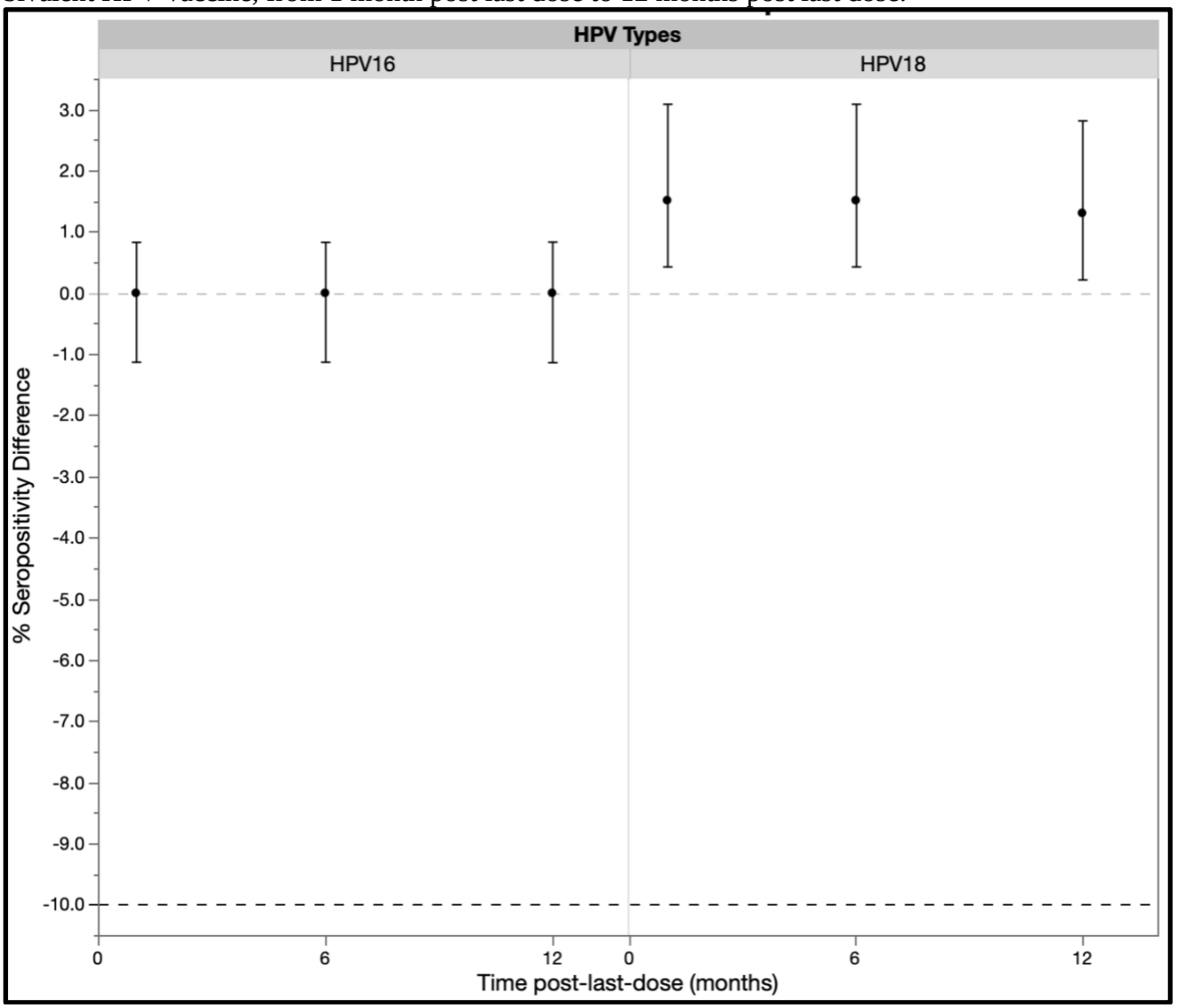
One month after administration of the last dose of HPVV, seroconversion to vaccine-type HPV for the 0, 12m schedule was non-inferior to that of the 0, 6m schedule when two doses of the bivalent or two doses of the nonavalent vaccines were administered (Figure 4). The bivalent vaccine also showed non-inferior seropositivity to vaccine-type HPV for the 0, 12m schedule compared to the 0, 6m schedule, and this persisted up to 1 year post-last-dose, which was the maximum duration of follow-up for which data was reported (Figure 5). No data were available to assess the immunogenicity of 0, 12m versus 0, 6m interval for two doses of the nonavalent vaccine beyond 1m post-last-dose. Contrasting to a regimen of two doses of bivalent or nonavalent vaccines, non-inferiority in vaccine-type HPV seroconversion was not demonstrated for a mixed quadrivalent-nonavalent regimen, when the two doses were administered at a 0, 36-96m interval versus a 0,6m interval (Figure 4). The very wide confidence intervals for seroconversion difference based on data reported for this mixed schedule included the non-inferiority margin of -10% difference in seroconversion for all four HPV types (6/11/16/18) and above 0.0%, even though the point estimates were 0.0% (95% CI: -11.07%, 2.18%). The point estimate and confidence intervals suggest that seroconversion could be worse, better or no different, and so this study is inconclusive in regards to the relative effects of 0,36-96m versus 0,6m schedules on the seroconversion rates for HPVVs. Further, no data is currently available beyond 1m post-last-dose, as such the seroconversion difference between schedules of 0,36-96m and 0,6m for this regimen could not be assessed over time. There was also no indication of heterogeneity in seroconversion across the studies ($I^2=0$).

Figure 4: Difference in seroconversion to vaccine type HPV strains between two-dose schedules administered at 0,7+m versus 0,6m, at 1m after last HPV vaccine dose.



2v=bivalent vaccine, 4v=quadrivalent vaccine, 9v=nonavalent vaccine, squares = mixed schedule of quadrivalent and nonavalent HPV vaccine reported by Gilca et al (2019), triangles = two doses of nonavalent vaccine reported by the nonvalent study[81], circles= 2 doses of bivalent vaccine reported by the bivalent study[80]. The line at -10% is the pre-specified non inferiority margin for the ratio of the 0, 7+m interval group versus 0, 6m interval group. The line at 0 represent no difference. 95% Confidence Interval were calculated using Wilsons exact approach without continuity correction.

Figure 5: Trend in seropositivity difference of 12m versus 6m intervals between two doses of bivalent HPV vaccine, from 1 month post last dose to 12 months post last dose.

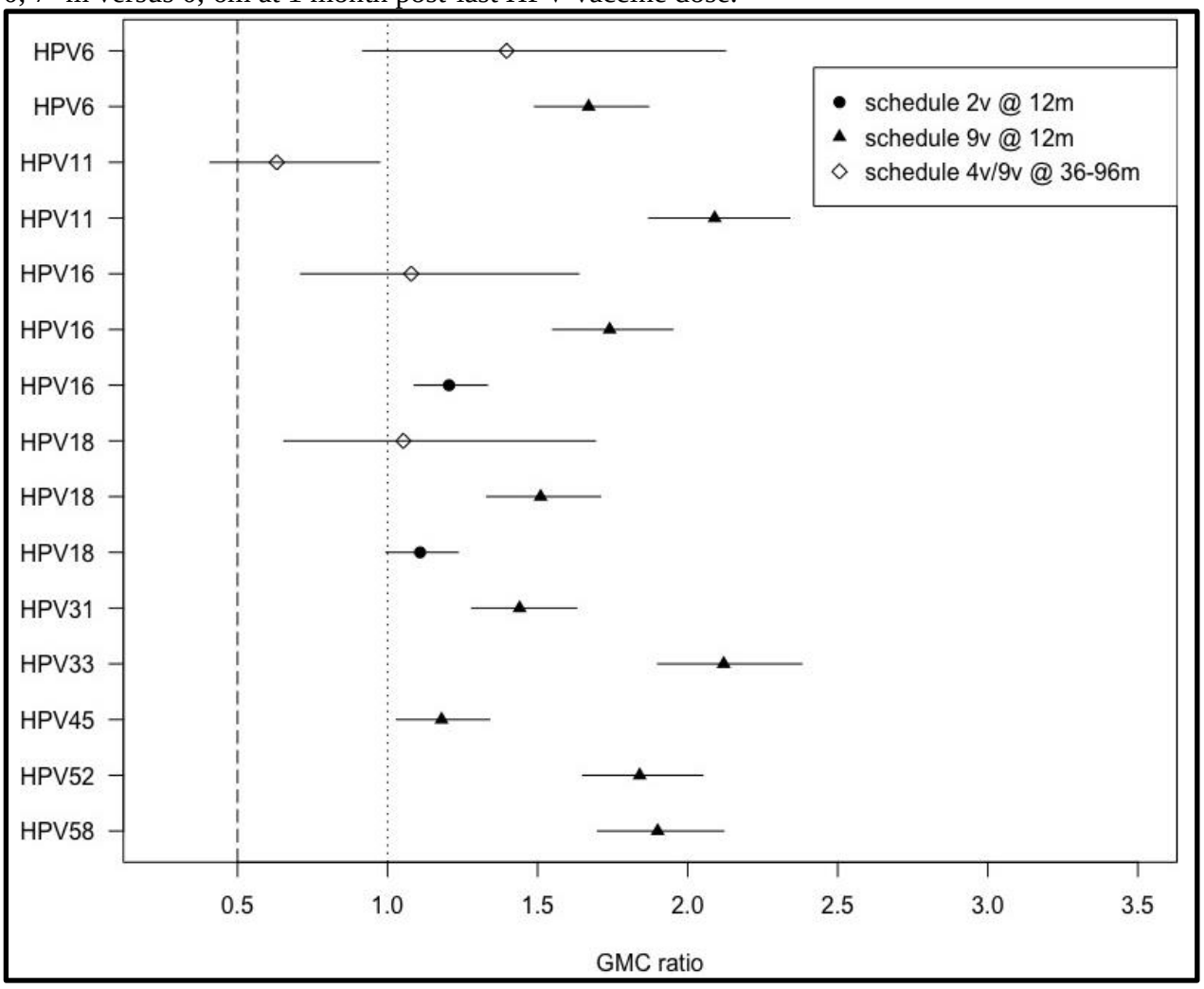


Grey line indicates no difference and the black line indicates the -10% non-inferiority margin.

Antibody levels

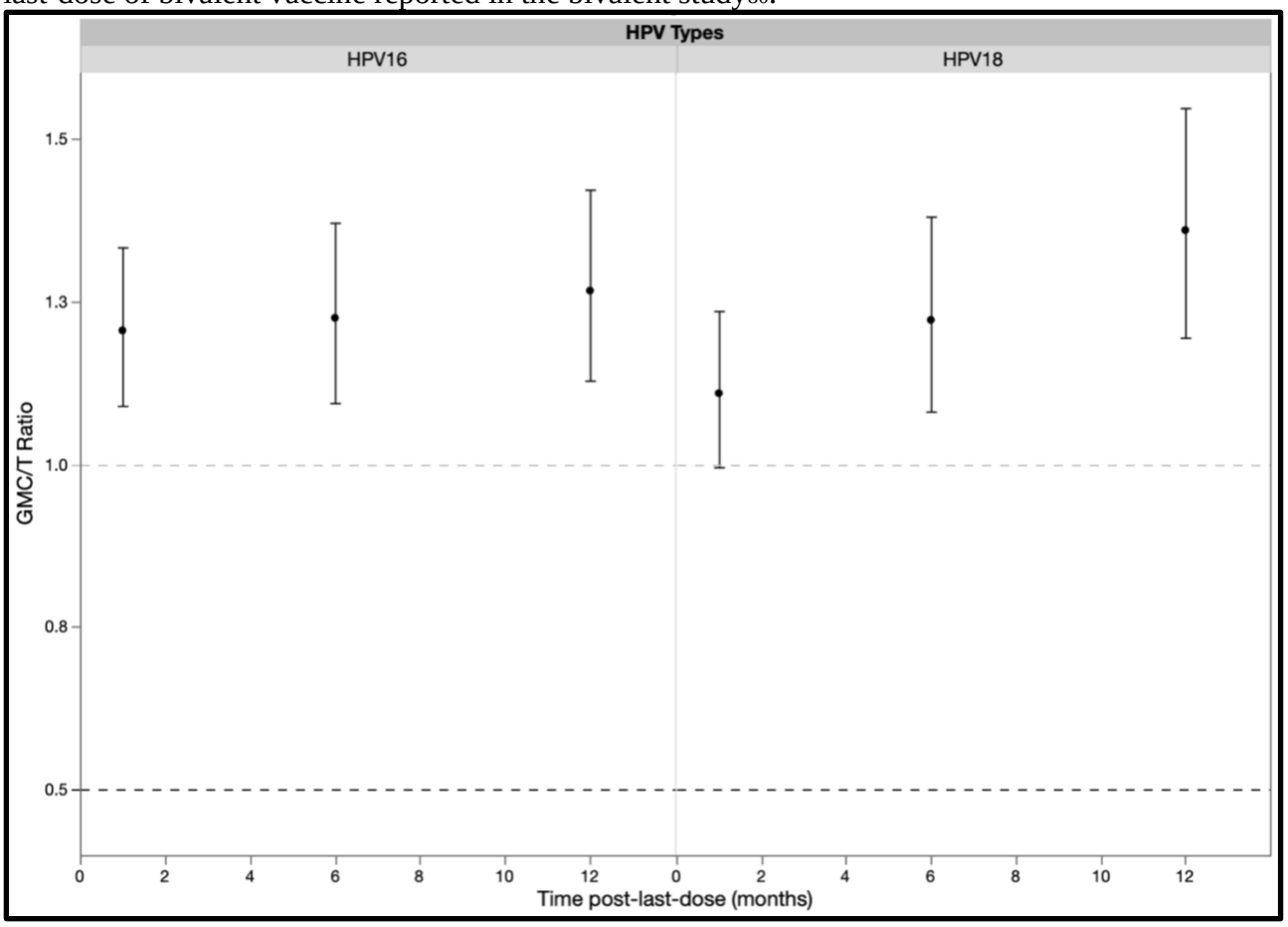
At one month post-last-dose of HPVV, a 12m interval between two doses of bivalent or nonavalent vaccine was superior to a 6m interval in antibody response to almost all vaccine-type HPV. This superiority was demonstrated since the lower limit of the confidence intervals of 12m to 6m geometric mean concentration or titer (GMC/T) ratios exceeded 1 for all vaccine-types, except for HPV18 when the bivalent vaccine was administered (GMC/T ratio 1.11, 95%CI: 1.00 to 1.23, Figure 6). GMC/T ratios for HPV16 and 18 for the bivalent and nonavalent vaccines showed substantial heterogeneity for the ratio of the peak antibody response at 1m post-last-dose (I_2 = 76%), precluding pooling of these data. The 12m interval provided antibody responses superior to the 6m interval for HPV16 and 18 at 6-12m post-last-dose for the bivalent vaccine (Figure 7). A two dose interval of 36-96m between doses was non-inferior to a 6m interval in antibody response to HPV6, 16 and 18, but not HPV11 (GMC/T ratio 0.63, 95%CI: 0.41 to 0.97, Figure 6). Estimates of the GMC/T ratio for 0, 36-96m vs 0, 6m based on the mixed vaccine schedule reported by Gilca et al 2019 were the lowest among the three studies. The confidence intervals were also the widest of the three studies. This imprecision is not surprising considering the small number of study participants (31) in the 0, 36-96m treatment arm.

Figure 6: Vaccine type HPV antibody ratios for two dose schedules administered at intervals of 0, 7+m versus 0, 6m at 1 month post-last HPV vaccine dose.



2v=bivalent vaccine, 4v=quadrivalent vaccine, 9v=nonavalent vaccine, squares = mixed schedule of quadrivalent and nonavalent HPV vaccine reported by Gilca et al (2019), triangles = two doses of nonavalent vaccine reported by the nonvalent study[81], circles= 2 doses of bivalent vaccine reported by the bivalent study[80]. The line at 0.5 is the pre-specified non inferiority margin for the ratio of the 0, 7+m interval group versus 0, 6m interval group. The line at 1 represent no difference.

Figure 7: Variation in the antiHPV16 and antiHPV18 antibody response from 1-12 months post-last-dose of bivalent vaccine reported in the bivalent study[80].



Grey line indicates no difference and the black line indicates the 0.5 non-inferiority margin.

Cellular Response

Memory B-cell and T-cell immune response were measured in a subset of participants in the bivalent study. No CD8+ T cell response to HPV16/18 was detectable for any of the evaluated schedules. The memory B-cell and CD4+ T-cell response were of similar magnitude for the 0, 12m and 0, 6m schedules, at 36m post-dose-one. The study authors noted however, that the number of participants observed would not have provided sufficient statistical power to detect differences between the groups.

Effectiveness

Data on the effectiveness of extending the interval between two doses of HPVV in the two-dose schedule is limited. A total of eight HPV-related diseases were specified as outcomes of interest to assess the effect of the length of the dose interval in two-dose schedules on HPVV effectiveness. Data at this time was only available for AGWs as an outcome. This data was provided by one study, Lamb et al, that investigated the effect of time intervals of 4-7m and 8+m on AGW incidence. Increasing the interval between two doses, from 4-7m to 8+m was associated with an non-significant increase in AGW incidence rate, for females younger than 17 years (IRD 256.21, 95%CI -12.11, 524.53 per 100,000 person-years) as well as those aged 17-19 years (IRD 448.62, 95%CI -49.41, 946.64 per 100,000 person-years). These are inconclusive findings since they include both the non-inferiority margin as well as the margin of no difference.

GRADE Assessment

Assessment of inconsistency, indirectness and imprecision were based on the guidelines provided by Meader et al (2014) to improve consistency and reproducibility of GRADE assessments[85]. Effect estimates based on the bivalent and nonavalent vaccines were assessed to have high certainty due to them being RCTs with low risk of bias and sample sizes of over 100 participants per study group. Effect estimates based on Gilca et al and Lamb et al were assessed to be of low certainty due to their moderate risk of bias and wide confidence intervals. These are effects of their observational study design and in the case of Gilca et al, the small size of the 0,

36-96m group (31 participants) contributed greatly to the imprecision. The complete GRADE assessment is provided in Appendix 3.

Discussion

Immunogenicity

In this systematic review we investigated the effect of dose intervals of 0, 7+m versus 0, 6m on the immunogenicity and effectiveness of two doses of HPVVs. We found the effect to be dependent on: HPV type, HPVV and the length of the two-dose interval beyond 6 months. An interval of 12m generally improved the antibody response when compared to a 6m interval between two HPVV doses. This concurs with the report by Bergman et al 2020, that increasing the two dose interval from 0, 6m to 0, 12m increases immunogenicity [27]. The length of the interval between the prime and boost vaccine doses mediates the extent to which stimulation and maturation of antibody producing B-cells is achieved before boosting[44,86]. Compared to a 6m interval, a 12m interval would allow the processes involved in stimulation and maturation of antibody-producing B-cells to reach further completion before boosting. This could be a reason for the increased antibody response generally observed for 12m versus 6m intervals.

While a 12m two-dose interval was generally superior in antibody response to a 6m interval, a 36-96m two-dose interval was non-inferior for HPV6, 16, and 18, but not so for HPV11. It is notable that evidence for the 36-96m interval was drawn from a non-randomised study with at least moderate potential for confounding, a low sample size (31 individuals for the 0, 36-96m and 173 individuals for the 0, 6m) that gave inconclusive results for seroconversion difference (0.00%, 95% CI: -11.07%, 2.18%) and wide confidence intervals around the antibody response to the vaccine-type HPVs. Nevertheless, the non-inferiority of the extended 36-96m interval to a 6m interval for hrHPV types is encouraging in its potential to be used for vaccination programs against cervical cancer. The clinical significance of the HPV11 antibody response failing to

achieve non-inferiority when two doses are administered on a 36-96m schedule versus 0,6m schedule is unclear. As previously mentioned, a minimum antibody level required for protection against HPV infection has not been established[63], as well, the presence of memory B-cells may be enough to trigger a protective anamnestic response during natural HPV infection, even if plasma antibody levels become low or even undetectable post-vaccination [45,87]. Further studies are required to confirm the performance of the 36-96m interval.

Efficacy and Effectiveness

AGW was the only clinical outcome for which data was available to assess the impact of extending the two-dose intervals on HPVV efficacy or effectiveness. Non-inferiority analysis based on these data was however inconclusive with incidence rate difference of 256.21, 95%CI -12.11, 524.53 per 100,000 person-years.

There is a clear need for high quality empirical evidence to assess the impact of extending intervals for two-dose schedules beyond 6 and 12 months, on the performance of HPVV in relation to accepted primary end-points[51] for HPV diseases. Assessing efficacy or effectiveness of the HPV vaccine among 9-14 year olds using cervical samples is constrained by ethical considerations[51], since most in this age group have not initiated sexual contact. Perhaps AGW incidence could be explored as a proxy for efficacy and effectiveness among this age group. Lamb et al demonstrated this by investigating AGW incidence among 10-16 year olds using registries. More precise estimates should be pursued.

Strengths and Limitations

This systematic review was executed according to a previously published protocol and focuses on the effect of extending dose intervals beyond six months on the two-dose HPV vaccine schedule. It was comprehensive in the search for eligible studies based on the range of databases queried. In regards to its focus, this review is more comprehensive than Bergman et al (2020) since it incorporates all available randomised and non-randomised studies comparing the effect of intervals of 6m or longer on HPVV immunogenicity and clinical outcomes. Including insights from additional sources is especially important given the limited reported data examining the effect of increased intervals between two HPVV doses. It is also a recommended practice[88,89] and for this review it provided more nuanced insights into the effect of dose intervals greater than 6m. A poignant concern with including non-randomised studies in systematic reviews, is their potential for increased risk of bias. With this in mind, we qualitatively incorporated insights from non-randomised and randomised studies, rather than pooling data across study designs[71,90]. It is notable that two studies included in this review, the nonavalent study by Merck and Gilca et al, included males 9-14 years as study participants. This is acceptable, as HPV vaccine antibody response has not been shown to be sex-dependent[36,57,91]. Comparison of vaccine schedules have been done using time post-dose-one and time post-last-dose. This study used time post-last-dose only, as it reveals the true time-matched relative effects of schedules with different dose intervals. Rather than comparing absolute antibody measures, we generated relative measures between the 0,7+m and 6m time intervals and compared these relative measures. In so doing we would have minimised the influence of between-study methodological variations on the inferences generated. A less than ideal step of our methodology, was the performance of the ROBINS-I assessment by a single team member (MPH candidate). The ROBINS-I was intended to completed by a panel of content and methodological experts related to the review[75]. The risk

of bias report generated by the single reviewer, was however evaluated by a senior member of the review team and no change in judgements were deemed necessary.

This systematic review was limited by the scarcity of data on the effects of extended intervals longer than 6m on the immunogenicity, efficacy or effectiveness of two-dose HPVV schedule. Further, the studies of immunogenicity included in this review included only participants of ages 9-14 years, so while our data will be relevant to the primary target group for HPV vaccination (females 9-14 years) and boys of that age, it may not be generalizable to older females.

Implications and Recommendations for Public Health Practice

The minimal immune correlates necessary for protection against HPV infection remains unknown, however, antibody response is an essential component of the protection against HPV infection. The findings of non-inferior immunogenicity for hrHPV types after extended dosing of the two-dose schedule are particularly encouraging for public health, and have implications for HPV schedule recommendations.

First, the generally greater immunogenicity when the two-dose interval is 12m versus 6m suggests that 0,12m could safely be promoted as the preferred dosing interval in HPVV dose recommendations, rather than 0,6m. This is especially true if a 12m interval can truly deliver added benefits in ease or costs of vaccine administration to the primary target population (females 9-14 years). Most Canadian provinces, including British Columbia, currently use a 0,6m two-dose schedule in their school-based HPV vaccination programs[20]. Moving to a 0,12m schedule would reduce the number of school visits that health-care professionals must make each year to administer this vaccine. This could potentially improve the cost-effectiveness of the HPV vaccination programs.

It is unlikely however, that a 0,12m schedule would provide substantial alleviation of the current shortfall in HPVV supplies. Suggestions have been made for the two-dose interval to be extended to 3-5 years between doses[28]. The non-inferiority of HPV16 and 18 at a 36-96m interval compared to a 6m interval suggests that a 3-5 year interval between doses may perform acceptably among the primary target population. Considering that the study providing data for the 36-96m interval is of sub-optimal rigor, further investigation of this interval is justified to confirm whether it is sufficiently protective against HPV infection and pre-cursors to cervical cancer.

Conclusion

The evidence indicates non-inferiority of 0, 12 month schedules to 0, 6m schedules in immunogenicity to all HPV types. Also the 0, 36-96m schedule is non-inferior to HPV6, 16, 18 but not HPV11. These findings support the use of HPVVs in two-dose schedules with extended intervals of 12 months for females and males 9-14 years of age and provides vaccination programs more flexibility in regards to the time for administering the second immunization. The non-inferiority of 36-96m to 6m for HPV6, 16 and 18 is promising but needs further confirmation since these findings were obtained from observational data in a study with a small sample size and have low certainty. The data available did not allow assessment of the effect of the extended interval (0,7+m) on vaccine efficacy and effectiveness and underscores the need for further investigations with regard to the effectiveness of two-dose schedules with intervals longer than 6 and 12 months.

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APPENDICES

Appendix 1: Ovid Medline Search Strategy

#	Searches	Results	Annotations
1	(HPV or "Human Papillomavirus" or Papillomaviridae).ti,ab,kf. or exp Papillomaviridae/ or exp papillomavirus infections/pc	52663	
2	exp mass immunization/ or exp immunization/ or exp secondary immunization/ or immunization.ti,ab,kf.	217053	
3	Vaccin*.ti,ab,kf. or exp vaccination/ad, im or exp virus vaccine/	301028	
4	1 and (2 or 3)	12260	
5	exp papillomavirus vaccines/ad, im	3661	
6	((vaccin* adj3 (HPV or papillomavirus)) or (immuni#ation adj3 (HPV or papillomavirus))).ti,ab,kf.	9323	
7	4 or 5 or 6	12518	HPV vaccination
8	((vaccin* adj (schedul* or regimen* or "alternate schedul*" or "extended interval*" or "alternat* vaccination scheme*" or "dose interval*" or timing)) or immuni#ation schedul*).ti,ab,kf.	6077	
9	exp immunization schedule/ or exp time factors/	1165354	
10	7 and (8 or 9)	782	scheduling/timing
11	exp immunogenicity, vaccine/	936	
12	Immunogeni*.ti,ab,kf.	57093	
13	exp immunity, humoral/ or exp B-Lymphocytes/ or exp antibodies/ or exp antibodies, viral/ or exp antibodies, neutralizing/	859708	
14	("antibody response" or "B Lymphocyte*" or Bcell* or "B cell*" or humoral or antibod* or "geometric mean concentration*" or "geometric mean titer*" or "neutralizing antibod*").ti,ab,kf.	982553	
15	exp immunity, cellular/ or exp CD4-positive T-lymphocytes/ or exp T-lymphocytes/	392276	
16	("cellular immunity" or T-cell* or Tcell* or "T cell*" or "CD4-Positive T-Lymphocyte*" or T-Lymphocyte*).ti,ab,kf.	405999	
17	exp seroepidemiologic studies/	22389	
18	(seroprevalence or seropositi*).ti,ab,kf.	47770	
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1723431	immunogenicity
20	(efficacy or effectiveness).ti,ab,kf.	1109127	
21	(inciden* or prevalen* or persisten* or "HPV infection" or "Human papillomavirus infection").ti,ab,kf.	1728386	
22	exp papillomavirus infections/ or exp prevalence/	300674	
23	exp Uterine Cervical Neoplasms/ or exp cervical intraepithelial neoplasia/	73159	
24	("Cervical Intraepithelial Neoplasia" or CIN* or "cervical cancer" or "Uterine Cervical Neoplasm*").ti,ab,kf.	156333	
25	exp vaginal neoplasms/ or exp vulvar neoplasms/	12382	
26	("vaginal cancer*" or "vulvar* cancer").ti,ab,kf.	2181	
27	exp anus diseases/ or exp Anus Neoplasms/ or exp condyloma acuminata/	12214	
28	("anal cancer*" or "Anus Neoplasm*" or condyloma or "condylomata acuminat*" or "wart*").ti,ab,kf.	18026	
29	("penile cancer*" or "penile neoplasm*").ti,ab,kf.	1702	
30	exp penile neoplasms/	5253	
31	exp neoplasms/ or exp carcinoma, squamous cell/	3190228	
32	(Neoplasm* or "Squamous Cell Carcinoma").ti,ab,kf.	340483	
33	exp Oropharyngeal Neoplasms/ or exp "Head and Neck Neoplasms"/	297000	
34	("oropharyngeal cancer*" or "oropharyngeal neoplasm*" or (head and neck cancer*)).ti,ab,kf.	27829	
35	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	5713145	efficacy or effectiveness
36	10 and (19 or 35)	653	HPV vaccine alternate schedule and immunogenicity/efficacy/effectiveness)
37	exp animals/ not humans.sh.	4597048	
38	HIV.ti,kf.	198790	
39	(cost-effectiv* or "cost analysis").ti,kf.	32552	
40	("vaccin* hesitan*" or belief* or uptake or "vaccin* accepta*" or "vaccin* delivery" or coverage or "vaccin* refusal" or "therapeutic vaccin*").ti.	101183	
41	(editorial or letter or comment or review).pt. or ("position paper" or review* or comment*).ti.	4435095	
42	("psychosocial factor*" or knowledge or attitude* or awareness or education or "health communication").ti.	230261	
43	37 or 38 or 39 or 40 or 41 or 42	9257493	
44	36 not 43	419	final

Appendix 2a: Risk of Bias Assessment for Gilca et al 2019

Domain	Judgement	Reason
Bias due to confounding	Moderate	36-96m participants all vaccine non-compliant while 6m all compliant HPV vaccination coverage lower among socially deprived individuals in Quebec judgement reduced to moderate to reflect potential for indication bias
Bias in selection of participants	Moderate	36-96m participants are non-compliant vaccinees who consented to second dose no data provided on the proportion of those who consented or characteristics relative to those who did not judgement reduced to moderate to reflect potential for volunteer bias
Bias in classification of interventions	Low	only assessed HPV types present in both vaccines (HPV6,11,16,18)
Bias due to deviations from intended interventions	Low	no deviation reported
Bias due to missing data	Low	no data of interest missing
Bias in measurement of outcomes	Low	objective ELISA measurement so antibody level with defined cutoff for positive
Bias in selection of the reported result	Low	none detected
Overall	Moderate	Possibly favours 36-96m if HPV exposure higher in this group

Appendix 2b: Risk of Bias Assessment for Lamb et al 2017

Domains	Judgement	Reason
Bias due to confounding	Moderate	authors suggest potential for unknown confounder as 8+m AGW IR unexpectedly higher 10-16 years age group is inadequate to control for effect of age age structure within 10-16 years group not compared for 8+m and 4-7m
Bias in selection of participants	Low	all database entries meeting predefined selection criteria included
Bias in classification of interventions	Low	intervention 8+m vs 4-7m defined and not amendable by knowledge of outcome
Bias due to deviations from intended interventions	Low	no cointerventions
Bias due to missing data	Low	database lacks outcomes for undiagnosed or untreated participants both 8+m and 4-7m participants were vaccinated and expected to have similar likelihood of healthcare access
Bias in measurement of outcomes	Low	outcome defined prior to identification in database records
Bias in selection of the reported result	Low	IR reported for each pre-specified time-interval
Overall bias	Moderate	Favours 4-7m

Appendix 3: Table of GRADE assessment of the evidence in this systematic review

Outcome or sub-group	Certainty Assessment							
	According to Protocol Population	Study Design	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty of Evidence
HPV6 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	778	RCT	1	not serious	not serious	not serious	not serious	high
Quadrivalent then Nonavalent (0, 36-96m vs 0, 6m)	204	Obs	1	serious	not serious	not serious	serious	low
HPV11 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	779	RCT	1	not serious	not serious	not serious	not serious	high
Quadrivalent then Nonavalent (0, 36-96m vs 0, 6m)	204	Obs	1	serious	serious	not serious	serious	low
HPV16 Antibody Ratio at 1 month post-last-dose								
Bivalent vaccine (0, 12m vs 0, 6m)	794	RCT	2	not serious	not serious	not serious	not serious	high
Nonavalent vaccine (0, 12m vs 0, 6m)	809	RCT						
Quadrivalent then Nonavalent (0, 36-96m vs 0, 6m)	204	Obs	1	serious	not serious	not serious	serious	low

Appendix 3: Table of GRADE assessment of the evidence in this systematic review

Outcome or sub-group	Certainty Assessment							
	According to Protocol Population	Study Design	no. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty of Evidence
HPV18 Antibody Ratio at 1 month post-last-dose								
Bivalent vaccine (0, 12m vs 0, 6m)	817	RCT	2	not serious	not serious	not serious	not serious	high
Nonavalent vaccine (0, 12m vs 0, 6m)	810	RCT						
Quadrivalent then Nonavalent (0, 36-96m vs 0, 6m)	204	Obs	1	serious	not serious	not serious	serious	low
HPV31 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	811	RCT	1	not serious	not serious	not serious	not serious	high
HPV33 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	813	RCT	1	not serious	not serious	not serious	not serious	high
HPV45 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	815	RCT	1	not serious	not serious	not serious	not serious	high

Appendix 3: Table of GRADE assessment of the evidence in this systematic review

Outcome or sub-group	Certainty Assessment							
	According to Protocol Population	Study Design	no. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty of Evidence
HPV52 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	813	RCT	1	not serious	not serious	not serious	not serious	high
HPV58 Antibody Ratio at 1 month post-last-dose								
Nonavalent vaccine (0, 12m vs 0, 6m)	805	RCT	1	not serious	not serious	not serious	not serious	high
Anogenital wart incidence								
Quadrivalent vaccine (0, 8+m vs 0, 4-7m)	13569	Obs	1	Serious	not serious	not serious	serious	low

Obs= observational study,

Appendix 4: Tables summarizing data used and relative effect measures generated

Table: Summary Data Table 1

Outcome or sub-group	Population	ATPP/n	Reported Outcome Measure 0, 7+m	Reported Outcome Measure 0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV6 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	257,521	257/257	F:257/258, M:263/263	0.19% (-1.28, 1.08)*	high
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	31/31	173/173	0.00% (-11.07, 2.18)	low
HPV11 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	257,522	257/257	F: 258/258, M:264/264	0.00% (-1.47, 0.73)*	high
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	31/31	173/173	0.00% (-11.07, 2.18)	low

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 2

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV16 Seroconversion difference (%) at 1 month post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	339, 455	339/339	455/455	0.00% (-1.12, 0.84)	high
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	264, 545	264/264	F: 272/272, M:273/273	0.00% (-1.44, 0.70)*	
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	31/31	173/173	0.00% (-11.07, 2.18)	low
HPV16 Seropositivity difference (%) at 6 months post-lastdose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	339, 455	339/339	455/455	0.00% (-1.12, 0.84)	high
HPV16 Seropositivity difference (%) at 12 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	337, 453	337/337	453/453	0.00% (-1.13, 0.84)	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 3

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV18 Seroconversion difference (%) at 1 month post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	355, 462	355/355	455/462	1.52% (0.44, 3.10)	high
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	266, 544	266/266	F: 272/272, M: 272/272	0.00% (-1.43, 0.70)*	
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	31/31	173/173	0.00% (-11.07, 2.18)	low
HPV18 Seropositivity difference (%) at 6 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	355, 462	355/355	455/462	1.52% (0.44, 3.10)	high
HPV18 Seropositivity difference (%) at 12 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	353, 459	353/353	453/459	1.31% (0.22, 2.82)	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 4

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	0, 6 m	Effect estimate (95% CI).	Certainty of Evidence
HPV31 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 543	268/268	F:271/272, M:271/271	0.18% (-1.23, 1.04)*	high
HPV33 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	269,544	269/269	F:272/273, M:271/271	0.18% (-1.23, 1.03)*	high
HPV45 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 547	268/268	F:272/274, M:271/273	0.73% (-0.69, 1.87)*	high
HPV52 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 545	268/268	F: 271/272, M: 273/273	0.18% (-1.23, 1.03)*	high
HPV58 Seroconversion difference (%) at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	265, 540	265/265	F:270/270, M:270/270	0.00% (-1.43, 0.71)*	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 5

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	Reported Outcome Measure 0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV6 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	257, 258 + 263	2678.8 (2390.2, 3002.1)	F:1657.9 (1479.6, 1857.6), M: 1557.4 (1391.5, 1743.1)	1.67 (1.49, 1.87)*	high
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	1640.5 (1094.7, 2458.3)	1174.5 (1049.0, 1315.3)	1.40 (0.92, 2.13)	low
HPV11 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	257, 258 + 264	2941.8 (2626.6, 3294.9)	F: 1388.9 (1240.4, 1555.3), M: 1423.9 (1273.2, 1592.3)	2.09 (1.87, 2.34)*	high
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	374.7 (246.6, 569.1)	593.9 (527.7, 668.3)	0.63 (0.41, 0.97)	low

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 6

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	Reported Outcome Measure 0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV16 Antibody Ratio at 1 month post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	339, 455	11329.4 (10509.3, 12213.5)	9402.9 (8792.4, 10055.8)	1.20 (1.09, 1.33)	high
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	264, 272 + 264	14329.3 (12796.4, 16045.9)	F: 8004.9 (7160.5, 8948.8), M: 8474.8 (7582.4, 9472.3)	1.74 (1.55, 1.95)*	
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	405.5 (271.6, 605.3)	375.9 (334.6, 422.2)	1.08 (0.71,1.63)	low
HPV16 Antibody Ratio at 6 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	339, 455	3248.2 (2974.2, 3547.4)	2653.5 (2473.5, 2846.6)	1.22 (1.09, 1.37)	high
HPV16 Antibody Ratio at 12 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	337, 453	2191 (2003.9, 2395.5)	1730.7 (1608.6, 1862.0)	1.27 (1.13, 1.42)	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 7

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV18 Antibody Ratio at 1 month post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	355, 462	6580 (6075.8, 7126.0)	5935.6 (5519.4, 6383.3)	1.11 (1.00, 1.23)	high
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	266, 272 + 272	2810.4 (2474.9, 3191.3)	F: 1872.8 (1651.6, 2123.6), M: 1860.9 (1641.1, 2110.2)	1.51 (1.33, 1.71)*	
4v then 9v (0,36-96m vs 0,6m)	F & M 9-14 yrs	31, 173	552.9 (348.5, 877.2)	525.2 (470.1, 586.8)	1.05 (0.65, 1.69)	low
HPV18 Antibody Ratio at 6 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	355, 462	1860.3 (1699.4, 2036.4)	1523.6 (1403.7, 1653.7)	1.22 (1.08, 1.38)	high
HPV18 Antibody Ratio at 12 months post-last-dose						
2v vaccine (0,12m vs 0,6m)	F 9-14 yrs	353, 459	1174.7 (1067.1, 1293.2)	864.6 (793.1, 942.7)	1.35 (1.19, 1.55)	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 8

			Reported Outcome Measure			
Outcome or sub-group	**Population**	**No. ATPP 7+m, 6m**	**0, 7+m**	**0, 6 m**	**Effect estimate (95% CI)**	**Certainty of Evidence**
HPV31 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 272 +271	2117.5 (1873.7, 2393.1)	F: 1436.3 (1272.1, 1621.8), M: 1498.2 (1326.5, 1692.0)	1.44 (1.28, 1.63)*	high
HPV33 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	269, 273 + 271	2197.5 (1961.9, 2461.3)	F: 1030.0 (920.4, 1152.7), M: 1040 (928.9, 1164.3)	2.12 (1.9, 2.38)*	high
HPV45 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 274 + 273	417.7 (365.9, 476.9)	F: 357.6 (313.7, 407.6), M: 352.3 (309.0, 401.7)	1.18 (1.03, 1.34)	high

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group

Table: Summary Data Table 9

Outcome or sub-group	Population	No. ATPP 7+m, 6m	Reported Outcome Measure 0, 7+m	0, 6 m	Effect estimate (95% CI)	Certainty of Evidence
HPV52 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	268, 272 +273	1123.4 (1008.1, 1251.9)	F: 581.1 (521.9, 647.1), M: 640.4 (575.2, 713)	1.84 (1.65, 2.05)*	high
HPV58 Antibody Ratio at 1 month post-last-dose						
9v vaccine (0,12m vs 0,6m)	F & M 9-14 yrs	265, 270 + 270	2444.6 (2185.2, 2734.9)	F: 1251.2 (1119.6, 1398.4), M: 1325.7 (1186.2,1481.6)	1.90 (1.70, 2.12)*	high
Incidence rate difference of Anogenital warts						
4v vaccine (0, 8+m vs 0, 4-7m)	F 10-16 yrs	1894, 8095	351 (168, 737)	84 (66, 108)	256.21 (-12.11, 524.53)[#]	low
	F 17-19 yrs	615, 2965	603 (271, 1343)	154 (69, 344)	448.62 (-49.41, 946.64)[#]	

2v= bivalent vaccine, 4v=quadrivalent vaccine, 9v= nonavalent vaccine, ATPP= according-to-protocol; population, F= female, M=male, *=based on pooling data for female and males as a single 0,6m group, [#]= per 100,000 person-years

Appendix 5: References for Publications Included in Systematic Review

1. Bivalent study
A Phase III Study of a 2-dose Regimen of a Multivalent Human Papillomavirus (HPV) Vaccine (V503), Administered to 9 to 14 Year-olds and Compared to Young Women, 16 to 26 Years Old (V503-010) - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01984697. Accessed March 25, 2020.

2. Nonavalent study
Evaluation of Immunogenicity and Safety of Two 2-dose Human Papillomavirus (HPV) Vaccine Schedules in 9-14 Year Old Girls - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01381575. Accessed March 25, 2020.

3 Gilca et al 2019
Gilca V, Sauvageau C, Panicker G, et al. Long intervals between two doses of HPV vaccines and magnitude of the immune response: A post-hoc analysis of two clinical trials. *Human Vaccines & Immunotherapeutics*. 2019;0(0):21645515.2019.1605278-21645515.2019.1605278. doi:10.1080/21645515.2019.1605278

4. Lamb et al 2017
Lamb F, Herweijer E, Ploner A, et al. Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: A nationwide cohort study. *BMJ Open*. 2017;7(6):1-7. doi:10.1136/bmjopen-2016-015021