Evidence based recommendations on Human Papilloma Virus (HPV) Vaccines Schedules

Background paper for SAGE discussions

March 11, 2014

TABLE OF CONTENTS

1. INTRODUCTION

The WHO's Strategic Advisory Group of Experts (SAGE) on Immunization has requested the WHO Secretariat to review the evidence concerning the optimal HPV immunization schedules.

Preparatory to such a review of the evidence by SAGE, it was deemed necessary to:

- systematically review all published and grey literature concerning schedules for HPV vaccines for adolescent girls in different epidemiological settings
- critically appraise the evidence using the WHO SAGE guidelines.

Methodology

Primary Question

The primary question of the review was what is the effect of a 2 dose HPV vaccine schedule compared with the licensed 3-dose schedule on immunological and clinical outcomes in pre-adolescent and adolescent girls?

The population included adolescent girls because this is the primary target group for primary vaccination. Data from both licensed bivalent and quadrivalent HPV vaccines were reviewed.

Sources of Evidence

This background paper for SAGE's consideration is informed by the data from the following four sources:

1. **Data presented during the *Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules* organized in Geneva, November 18, 2013**. All the principal investigators of randomized and non-randomized studies were invited to attend the consultation as well as representatives of the companies of the two currently licensed HPV vaccines.

   The meeting was open to all participants except for the session on conclusions and recommendations that was only attended by those participants who were deemed to have no or non-significant conflict of interest. Some of the unpublished or confidential information presented during this consultation have subsequently been made publicly available (as of February 2014) and are therefore included in this public report. (List of participants is available in Annex 1).

2. **Results from a systematic review conducted by an team of independent investigators[1].** The investigators systematically reviewed all published and grey literature concerning data comparing the effects of 2-dose and 3-dose HPV vaccination. All data available on randomized comparisons between girls (or women) of the same age and non-randomized comparisons between girls receiving 2-dose and women receiving 3-dose schedules in the literature and studies presented during the WHO Ad – hoc Expert Consultation are included in the companion document entitled ***HPV***

[1] D'Addario M et al. HPV vaccines: review of alternative vaccination schedules: Preliminary overview of the literature. Report to WHO 3rd March 2014 (unpublished update)

vaccines: review of alternative vaccination schedules (D'Addario M et al 2014)[1]***.*** The report of this systematic review is presented in Appendix 1.

3. **Results from non-systematic review of the data from observational studies**[2]. All data available on schedule comparisons from observational studies in the literature and studies presented at this WHO consultation were summarized by the WHO Secretariat. The summary of this review is presented in Appendix 2.

4. **The bivalent vaccine received approval for a pre-adolescent and adolescent indication to allow for administration of the vaccine according to an alternative 2-dose schedule (0, 6 months) in females aged 9-14 years old**. The European Medicines Agency (EMA)[3] report was made available in December 2013 providing public access to the evidence for this new indication. In February 2014, the EMA communicated the positive opinion of the Committee for Human Medical Products (CHMP) for an adolescent indication using the quadrivalent vaccine[4].

2. BACKGROUND

Human papillomavirus (HPV) causes cervical cancer which is the forth most common cancer in women worldwide by age-standardized incidence rate (ASR). In 2012, there were an estimated 528,000 new cases and 266,000 deaths due to cervical cancer. More than 85 % of cervical cancer deaths are in developing countries, where it accounts for 13% of all female cancers. Therefore, most of the burden of HPV-associated malignant and indeed benign disease is in developing countries without effective screening programmes and poor access to medical services.

Two vaccines are currently available, bivalent vaccine (Cervarix ®) and quadrivalent vaccine (GARDASIL®). Both were licensed with a 3 dose schedule at 0-(1 or -2)-6 months. Both are prepared from purified L1 protein, the major capsid protein that self-assembles to form type-specific HPV virus-like particles (VLPs). These VLPs closely resemble the outer surface of HPV virions. VLPs contain no viral DNA and are therefore non-infectious[5].

The quadrivalent vaccine was first licensed in the United States in 2006. The L1 proteins for each type are expressed via a recombinant Saccharomyces pombe (type of yeast) vector. Each 0.5 ml dose contains 20 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto 225 µg of the adjuvant, amorphous aluminium hydroxyphosphate sulfate (AAHS). The bivalent vaccine was first licensed in 2007. The L1 proteins for each type are expressed via a recombinant baculovirus (type of insect cell) vector. Each 0.5 ml dose contains 20 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto a proprietary AS04 adjuvant system containing 500 µg of aluminium hydroxide and 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A, a novel adjuvant.

---

[2] Non-systematic review of the data from observational studies: 2 versus 3 dose schedule (unpublished report by the WHO Secretariat)

[3] European Medicines Agency-Assessment Report-Cervarix. Procedure No. EMEA/H/C/000721/II/0048, 21 November 2013, EMA/789820/2013 Committee for Medicinal Products for Human Use (CHMP).

[4] htpp://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Assessement Report – Variation/human/000721/WC500160885.pdf

[5] WHO, The Immunological Basis for Immunization Series Module 19: Human papillomavirus infection(2011) http://whqlibdoc.who.int/publications/2011/9789241501590_eng.pdf?ua=1

Following a review of evidence and recommendations by SAGE at the November 2008 meeting, WHO issued a recommendation on the HPV vaccines in a Position paper that was published in 2009.[6]

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination of female adolescents should be included in national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

The 2009 WHO position paper (excerpts follow)[6] states that HPV vaccines are most efficacious in females who are naive to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The recommended primary target population is girls in the age range of 9-13 years. Vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, does not divert resources from vaccinating the primary target population or effective cervical cancer screening programmes, and if a significant proportion of the secondary target population is likely to be naive to vaccine-related HPV types. HPV vaccination of males is not recommended for the prevention of cervical cancer because vaccination strategies that achieve high coverage (>70%) in the primary target population of young adolescent girls are expected to be more cost effective in reducing cervical cancer than including the vaccination of males. Little information is available on the safety and immunogenicity of HPV vaccines in people who are immunocompromised due to medications or diseases. Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, they appear to be preserved[7] and the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer. Most target populations for HPV immunization are likely to include a few HIV-infected individuals, even in areas with a relatively low prevalence of HIV. Concerns about safety or reduced efficacy among females who may be infected with HIV should thus not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization. A need for booster doses has not been established, for either immunocompetent or immunocompromised individuals. Both vaccines should be administered according to their manufacturer's specifications, schedules and advice on interrupted schedules.

The WHO Global Advisory Committee for Vaccine Safety (GACVS) has reviewed the safety of HPV vaccines on several occasions (2007, 2008, 2009 and 2013). Evidence from all sources continues to support their conclusions about the safety of both vaccines. With more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, GACVS continued to be reassured by the safety profile of the available products.[8]

By the end of 2013, more than 40 countries had introduced HPV vaccine in their national immunization programmes (only three of them are developing countries). Most countries target vaccination at young girls (e.g. around 9 to 13 years of age) but there a few countries that also

[6] Human papillomavirus vaccines WHO position paper- April 2009 http://www.who.int/wer/2009/wer8415.pdf?ua=1

[7] Toft L et al 2013 ; Denny L, et al 2008

[8] GACVS Safety update on HPV Vaccines.Geneva, 13 June 2013.
http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf

offer the HPV vaccine to older girls (e.g. around 18 years of age) and women of reproductive age.

Although the cost per dose of vaccine has changed over time, current prices per dose for the PAHO revolving fund are USD $ 13.08 for bivalent vaccine and USD$ 13.79 for quadrivalent vaccine and, for GAVI procured vaccine through UNICEF Supply Division the prices are USD $4.50 and $4.60 respectively.

In addition to cost savings, there would be obvious programmatic advantages to reducing the number of doses (e.g. reduced delivery costs), and an increased flexibility of the intervals between doses (e.g. annual doses easier for school-based delivery) would probably also lead to increases in vaccination coverage.

3. USING IMMUNOGENICITY DATA TO INFORM POLICY RECOMMENDATIONS ON HPV SCHEDULES: CURRENT CHALLENGES

HPV vaccines were licensed based upon the demonstration of their clinical efficacy in young adult women. The age extension for adolescent girls, in whom efficacy trials would not be feasible, was granted because studies demonstrated that antibody responses in adolescent girls were not inferior to those elicited in women ("immunological bridging"). Alternative adolescent vaccine schedules should thus demonstrate that their immunogenicity is similarly non-inferior.

To seek licensing, a Phase III immunogenicity study of the quadrivalent HPV vaccine was conducted in adolescents with the objective of bridging the efficacy findings in young women to pre-adolescents and adolescents. The neutralizing anti-HPV GMTs at month 7 were non-inferior in adolescents - and indeed 1.7-2.7 fold higher than in the group of 16-23 year old females in whom efficacy was demonstrated[9] . Similar observations were made for the bivalent vaccine and for the nonavalent vaccines currently in clinical development.

The assumption is that the mechanism of protection afforded by the VLP vaccines is neutralizing antibody-mediated. This assumption is supported by animal models that demonstrate protection against viral challenge in animals immunized by passive transfer of hyperimmune serum from donors immunized with L1 VLPs[10] [11] [12]. Although immunization does elicit CD4+ T cells, their function is essentially to provide help to B cells. Effector T cells are important for HPV clearance following infection but are not considered as contributing to prophylactic vaccine efficacy as L1 is only expressed late during HPV infection.

Neutralizing antibodies are produced by plasma cells. The first wave of plasma cells elicited by priming results in the antibody peak observed 4 weeks later. Most of these plasma cells are short lived, such that peak antibody titers decline within a few months. However, some antibody-secreting cells become long-lived plasma cells. Long-lived plasma cells primarily reside in the bone marrow, continuously produce IgG antibodies and are responsible for long term antibody

[9] Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics. 2006;118(5 Nov):2135-45.

[10] Breitburd, F. et al., Immunization with virus like particles from cottontail rabbit papillomaviruses (CRPV) can protect against experimental CRPV infection. J Virol 69:3959-63.

[11] Suzich, JA. et al., Systematic immunization with papillomaviruses L1 protection completely prevents the development of viral mucosal papilloma. PNAS 1995;92(25):11533-11557

[12] Day, PM., In vivo mechanisms of vaccine-induced protection against HPV infection. Cell Host Microbe, 2010 Sep 16;8(3):260-70.

persistence. Different sub populations may survive for different lengths of time.[13] Antibody titers measured 12-18 months after the last dose of a VLP vaccine reflect the activity of long-lived plasma cells and are the best predictor of antibody persistence.

Circulating antibodies generated by L1 VLP vaccination are thought to reach the site of infection by active IgG transudation at least in the female genital tract, and by passive exudation at sites of trauma that are believed to be required for initiation of HPV infection.

Immunization also elicits memory B cells. Memory B cells (MBC) are resting cells, which do not secrete antibodies and so do not protect unless reactivated by antigen exposure and instructed to differentiate into antibody-secreting plasma cells (recall response). They reside mainly in the spleen but extra splenic niches exist. A small proportion of memory cells may be found in the blood. Although generated in parallel, the memory B cell and plasma cell compartments are independent. A study with the bivalent HPV vaccine reported that a significantly increased HPV 16 MBC population at day 210 after the 3rd dose of vaccine compared to that after the 2nd dose. HPV 18 specific MBC were increased after the 3rd dose but this was not significant[14]. Memory B cells elicited by HPV priming are assumed to mature into highly specific B cells which, when reactivated by vaccine boosting, differentiate into large numbers of long-lived plasma cells producing high levels of specific antibodies. For hepatitis B, memory B cells are assumed to be reactivated by viremia and thus contribute to the maintenance of protection after antibody decline. It is unclear whether memory B cells are reactivated by / contribute to long term protection after HPV VLP vaccination given that HPV infection is exclusively mucosal.

Thus, HPV antibody titers represent a valid marker to compare the expected clinical efficacy of various vaccines and schedules. VLP vaccines elicit very high antibody concentrations. Therefore, when different schedules are compared non-inferiority of antibody concentration must be achieved for alternative schedules if it is expected that the clinical efficacy will be equivalent.

Protective efficacy depends upon the quantity but also the quality of vaccine-induced antibodies. This quality is reflected by measure of the affinity of the antibodies for the antigen. With this avidity threshold, higher concentrations of antibody are needed for protection. After the first immunization(s) (priming), various B cells producing antibodies with a range of affinities for the vaccine antigens are generated. Only B cells with high affinity surface receptors can continue to capture scarce antigen, to interact with helper T cells and thus enter the long-lived plasma cell and memory pool. This process, called affinity maturation, requires several months (empirically a minimum of 4 months). These affinity-matured B cells (and the antibodies they produce) dominate the anamnestic response after the booster immunization. These higher affinity antibodies continue to compete for antigen and this selects B cells that can secrete even higher affinity antibodies. The combination of these multiple affinity interactions between antibodies and antigens is called avidity. Above a minimal avidity threshold, protection against viral challenge requires minimal antibody concentration. Strong 4 year protection was reported in Costa Rican women who received just one dose of bivalent vaccine. Also one dose recipients had avidities at month 36 that were almost as high as three dose recipients, although avidities one month after one dose (measured in women who eventually received three doses were

[13] Mamani Matsuda et al 2008 Blood 111;4653 and Ahuja et al 2008 PNAS 105;4802

[14] Giannini SL, Hanon E, Moris P, Van Mechelen M, Morel S, Dessy F, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. Vaccine. 2006;24(33-34):5937-49.

rather low). Some authors argued that the higher avidity B cell preferentially survived as long lived plasma cells, even after just a priming dose[15].

Also important, is the ability to prevent infection, as measured by in vitro neutralization assays. Early vaccines against denatured L1 failed in animal studies because they did not induce neutralizing antibodies. Correlations between neutralizing activity and avidity were not observed for individuals enrolled in the clinical trials (thus, suggesting that the antibody response in almost all individuals is above the threshold required for good neutralizing activity, although more data is needed on this).

The antibody responses are different after natural infection compared with HPV L1 VLP vaccination. After natural infection, 70-80% of women seroconvert and their antibody responses are typically slow, weak and of low avidity. But this is sufficient for antibodies generated in natural infections to be usually protective against subsequent incident infection. Following HPV L1 VLP vaccination, in contrast, close to 100% of women seroconvert after the first vaccine dose (priming). Peak antibody titers reach levels 10-1000 times greater than in natural infections and are of much higher avidity – i.e. protective capacity (ref). Neutralizing antibodies persist for >9 years post immunization (longer time point assessed) in women. These high-level and high-avidity antibody responses persist such that unquestionable to date, vaccine failures have not yet been identified in clinical studies, precluding the identification of a minimal antibody threshold level that correlates with the protection. No specific immune correlate is thus yet available.[16]

In addition to quantity and quality, kinetics are critically important for HPV-vaccine induced protection : 1) memory B cells elicited by the first vaccine dose require at least 4-6 months to mature and differentiate into high-affinity B cells. This implies that any immunization schedule must include at least a 4 month interval before the last dose (prime-boost) to efficiently reactivate memory B cells. Two dose schedules with shorter intervals (prime-prime) might not allow this affinity maturation and are expected to be less immunogenic / protective. 2) antibody persistence, i.e. the plateau of antibodies produced by long-lived plasma cells, is best estimated at least 6 months and preferably 12-18 months after the last immunization.

4. EFFECT OF VARIOUS IMMUNIZATION SCHEDULES ON VARIOUS OUTCOMES

Antibody concentration is the parameter currently used to assess HPV vaccine immunogenicity; as there is no defined immune correlate of protection. Clinical studies have demonstrated that both licensed HPV vaccines are generally well tolerated, immunogenic and efficacious using a 3 dose schedule (0, (1 or 2), 6 months).

Under current regulatory guidelines, efficacy has been assessed in women aged 15-25 years on disease endpoints (e.g. CIN2+, CIN3+) and virological endpoints (e.g. 6 or 12 months persistent infection at 6 months). These endpoints require invasive gynecological examinations/sampling and might be considered unethical in girls younger than 15 years of age. For both licensed HPV vaccines in girls 9-14 years of age efficacy has been inferred based on antibody immuno-bridging studies.

[15] Dauner JG Vaccine 28:5407-13, 2010 and J Schiller (personal communication on unpublished results that will be presented at the IVP meeting in Seattle, August 2014)

[16] Safaeian et al. 2010 JNCI:102;165; Harper et al Lancet 2006, 367,1247 and; Rowhani-Rahbar A et al. Vaccine 2009;27:5612-5619; Olsson et al. Vaccine. 2007

If bridging studies show that the immune response in the 9 to13-14 year old population is non-inferior to that of the 15-25 year old population, the efficacy of the vaccine is also expected to be similar in the two age groups. This principle is independent of the dosing schedule being assessed.

The interpretation of clinical trials or observational studies reporting vaccine efficacy after 2 versus 3 doses should take into account whether a 2-dose schedule included at least 4 months before the last dose (prime-boost) or not (prime-prime).

Evidence on the effect of fewer than 3 doses of HPV vaccine

Studies assessing 2-dose schedules versus 3-dose schedules[1]

Quadrivalent vaccine

- Two randomised controlled trials (Canada[17,18,19] and India[20,21]) comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls.
- One study provides additional results about immunological outcomes from a within-person comparison of girls (Canada[22]).
- A cohort study in Australia[23] assessing the risk of cervical abnormalities among women ≤ 17 year of age,vaccinated at school.
- A cross-sectional study in Victoria, Australia[24] -the Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE) study- assessing HPV vaccine-related infection and disease (CIN3) outcome.
- A cohort study using individual-level data in Sweden[25] assessing genital warts (GW) incidence after on-demand vaccination in girls and women aged 10 to 44 years living in Sweden between 2006 and 2010.
- A population based study in Sweden[26] examining the association between HPV vaccination and first occurrence of condyloma acuminata in relation to vaccine doses received.

---

[17] Dobson, S.R., et al., *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* JAMA, 2013. **309**(17): p. 1793-1802.

[18] Krajden, M., et al., *Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two- versus three-dose HPV vaccine trial.* Clin Vaccine Immunol, 2011. **18**(3): p. 418-23.

[19] Sankaranarayanan, R., *2 vs 3 doses HPV vaccine schedule: low- and middle-income countries*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.

[20] Sankaranarayanan, R. Trial of Two versus Three Doses of Human Papillomavirus (HPV) Vaccine in India. 2013 [cited 2013 Nov 15]; Available from: http://clinicaltrials.gov/show/NCT00923702.

[21] Sankaranarayanan, R., Evaluation of Fewer Than Three Doses of HPV Vaccination in India, in WHO Consultation Meeting. 2013: WHO, Geneva.

[22] Institut National de Santé Publique du Québec. *La vaccination des pré-adolescents contre les virus du papillome humain (VPH) au Québec : deux ou trois doses?* 2013 [cited 2013 Nov 14]; http://www.inspq.qc.ca/pdf/publications/1683_VaccinPreAdoVPHQc_2ou3Doses.pdf.

[23] Gertig, D.M., et al., Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med, 2013. 11(1): p. 227

[24] Garland, S.M., et al. Measures of vaccine effectiveness. Abstract no. SS 22-7 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy

[25] Leval, A., et al., Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst, 2013. 105(7): p. 469-74.

- A population based study in Denmark[27] assessing the association between receipt of at least one dose of HPV vaccine and its effect on risk of genital warts.
- A case control study in Australia[28] estimating the effectiveness of the vaccine in women partially (one or two doses) vaccinated or fully vaccinated (≥ 3 doses).

Bivalent vaccine

- One randomised controlled trial Canada/Germany1[29 30 31] comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls.
- Three non-randomised controlled trials, Canada/Germany29 30 31, Mexico[32], Multinational2[33 34 35] comparing a 2-dose schedule in girls with a 3-dose schedule in women.
- Two additional studies also reported on immunological outcomes. A study including randomised comparisons of women (Europe[36]) and, an observational study of girls (Uganda)[37].
- Two additional clinical trials reporting data about clinical outcomes from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (Costa Rica[38 39 40] and Multinationalx[41 42]). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months.

---

[26] Herweijer, E., Association of Varying Number of Doses of Quadrivalent Human Papillomavirus Vaccine With Incidence of Condyloma. JAMA. 2014;311(6):597-603. doi:10.1001/jama.2014.95.

[28] Crowe, E. et al., Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014;348:g1458.

[29] Romanowski, B., et al., Immune response to the hpv-16/18 as04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[30] Romanowski, B., et al., Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin, 2011. 7(12): p. 1374-86.

[31] GlaxoSmithKline. *Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 – 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing.* 2013 [cited 2013 Nov 14]; Available from: http://download.gsk-clinicalstudyregister.com/files/ebe3f40a-ef27-469c-8874-35053b5a80d7

[32] Lazcano-Ponce, E.S., M.; Muñoz, N.; Torres, L.; Cruz-Valdez, A.; Salmerón, J.; Rojas, R.; Herrero, R.; Hernández-Ávila, M, Overcoming barriers to HPV vaccination: Non-inferiority of Antibody Response to Human Papillomavirus 16/18 Vaccine in Adolescents Vaccinated with a Two-dose vs. a Three-dose Schedule at 21 Months. Vaccine 32 (2014) 725-732..

[33] EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix* 2013 21st November 2013.

[34] GlaxoSmithKline. Immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 L1 AS04 vaccine when administered according to alternative 2-dose schedules in 9 - 14 year old females. 2013 [cited 2013 Nov 14]; Available from: http://download.gsk-clinicalstudyregister.com/files/1ae03c85-a5fe-4339-a1e1-03a3d97f6793.

[35] Puthanakit, T., et al., Immune responses to a 2-dose schedule of the hpv-16/18 as04-adjuvanted vaccine in girls (9-14) versus 3 doses in women (15-25): a randomised trial, in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[36] Esposito, S., et al., Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study. Pediatr Infect Dis J, 2011. 30(3): p. e49-55.

[37] Safaeien, M., Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda, in 28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326. 2012: San Juan, Puerto Rico. p. 326.

[38] EMA. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix 2013 21st November 2013.

[39] Kreimer, A.R., et al., Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol., 2011. 12(9): p. 862-70. doi: 10.1016/S1470-2045(11)70213-3. Epub 2011 Aug 22.

[40] Kreimer, A.R., et al., Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst, 2011. 103(19): p. 1444-51.

One additional RCT providing data for women aged 15-25 years[43, 3,4] . This trial in Europe (Italy, Romania, and Slovakia) compared two 3-dose schedules (extended: 0, 1, 12 months vs. standard: 0, 1, 6 months). For the extended schedule, data are available at month two (one month after the second dose) and compared with month seven (one month after the third dose of the standard schedule).

Summary of studies assessing 2-dose schedule versus 3-dose schedules[1]

Quadrivalent vaccine	Bivalent vaccine
Geometric mean antibody concentrations	
In randomised comparisons: ○ for HPV16, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior compared with the 3-dose group in Canada17 18 19 . ○ in India[19,20,21] the ratio of antibody levels was higher in the 2-dose group. For HPV18 the GMC in the 2-dose group is non-inferior to that in the 3-dose group. ○ at 24 months, results from Canada17 18 19 were lower in the 2-dose group for both HPV16 and 18 and the lower 95% confidence interval included the non-inferiority margin. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18. ○ The weighted mean difference for the GMC in girls receiving the 2-dose schedule in Canada17 18 19 is non-inferior to the 3-dose schedule. Results are inconclusive for the other measured outcomes. ○ at 36 months, the GMC ratio for HPV16 was non-inferior (0.81. 95% CI 0.55, 1.20) and inconclusive for HPV18 (0.43, 95% CI 0.26, 0.73). ○ in the India20 21 trial, comparisons favoured the 2-dose schedule. The weighted mean differences correspond to a mean fluorescence index for HPV16 of 1.2 (1.0, 1.2) and for HPV18 1.0 (1.0, 1.2)	In the randomised comparison: ○ for HPV16, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior compared with the 3-dose group In Canada/Germany29 30 31. The lower bound of the confidence interval is below that non-inferiority margin but the upper bound is above it so the result is inconclusive. ○ for HPV18 the GMC in the 2-dose group is non-inferior to that in the 3-dose group. ○ at 24 months, results from Canada/Germany29 30 31 were lower in the 2-dose group for both HPV16 and 18 and the lower 95% confidence interval included the non-inferiority margin. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18 for HPV16 in Canada/Germany. In non-randomised comparisons, ○ GMCs were non-inferior or superior in girls receiving the 2-dose schedule compared with women receiving the 3-dose schedule in all four trials at all-time points assessed, up to 24 months after vaccination. ○ immunogenicity results showed that a 2-dose schedule of bivalent vaccine administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years at all-time points tested up to month 48[4]. In addition, exploratory or post-hoc analyses of vaccine efficacy at month 48 after the first vaccine dose among

[41] EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix* 2013 21st November 2013.

[42] Arguedas, A., et al., *Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines.* Vaccine., 2010. **28**(18): p. 3171-9. doi: 10.1016/j.vaccine.2010.02.045. Epub 2010 Feb 26.

[43] Esposito, S., et al., Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study. Pediatr Infect Dis J, 2011. 30(3): p. e49-55

Quadrivalent vaccine	Bivalent vaccine
	women aged 18-25 years who received only two doses demonstrate that two doses effectively protect against persistent infection due to HPV-16/18 combined (VE: 100 % [33.1%; 100] and 84.1% [50.2%; 96.3%][4] . Comparisons in women (Europe36), an observational study of girls (Uganda37) had overall findings about immunological outcomes that support those reported above. In the Europe36 trial, the investigators compared women one month after receiving two doses (of an extended 3-dose schedule) at 0, 1 month and women one month after receiving the licensed schedule (0, 1, 6 months). In this comparison of GMCs, the 2-dose schedule was inferior to the 3-dose schedule (weighted mean difference HPV16, -1.17, 95% CI -1.30, -1.05; HPV18, -0.53, 95% CI -0.66, -0.39).
Seroconversion and seropositivity	
Seroconversion and seropositivity, assessed in Canada17 18 19 were non-inferior at all-time points assessed except at 24 and 36 months in Canada17, 18, 19, when they were inconclusive.	Seroconversion and seropositivity, assessed in Canada/Germany29 30 31 were non-inferior at all-time points assessed. In non-randomised comparisons, available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule.
Clinical Outcomes	
The RCT in India20 21 provided limited data about clinical outcomes: incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.	In non-randomised comparisons, there were no clinical outcome data available for these four controlled trials. Data about clinical outcomes come from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (Costa Rica38 39 40 and Multinationalx41 42). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months. The results supported the 2-dose schedule. The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of vaccine in a trial in Europe (Italy, Romania, Slovakia) as observed at month 48 (end-of-study analysis) indicates that the HPV-16/18 vaccine also prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course[4].

Quadrivalent vaccine	Bivalent vaccine
Observational studies	
In the cohort study (Australia23) detection rates of histologically confirmed high-grade (HG) cervical abnormalities and high-grade cytology (HGC) were significantly lower for vaccinated women (any dose) (HG 4.8 per 1,000 person-years, HGC 11.9 per 1,000 person-years) compared with unvaccinated women (HG 6.4 per 1,000 person-years, HGC 15.3 per 1,000 person-years) HR 0.72 (95% CI 0.58 to 0.91) and HR 0.75 (95% CI 0.65 to 0.87), respectively. The HR for low-grade (LG) cytological abnormalities was 0.76 (95% CI 0.72 to 0.80). Vaccine effectiveness adjusted a priori for age at first screening, socioeconomic status and remoteness index, for women who were completely vaccinated, was greatest for CIN3+/ adenocarcinoma in situ (AIS) at 47.5% (95% CI 22.7 to 64.4) and 36.4% (95% CI 9.8 to 55.1) for women who received any dose of vaccine, and was negatively associated with age. In an interim analysis of the cross-sectional study in Victoria, Australia[24] 395 subjects for sub-study A, the prevalence of HPV16 was only 1.6% (95%CI 0.6-3.5%) and for any high risk HPV type was 14.4% (11.0 18.4%). No HPV18 was detected. Eighty one percent of the cohort was fully vaccinated. In the cohort study in Sweden25 vaccine effectiveness was 76% (95% CI = 73% to 9%) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (effectiveness = 93%, 95% CI = 73% to 98%). In the population based study in Sweden26 among those individuals aged 10 to 16 years at first vaccination, receipt of 3 doses was associated with an IRR of 0.18 (95%CI, 0.15-0.22) for condyloma, whereas receipt of 2 doses was associated with an IRR of 0.29 (95%CI, 0.21-0.40). The number of prevented cases between 3 and 2 doses was 59 (95%CI, 2-117) per 100 000 person-years. A maximum reduction in condyloma risk was seen after receipt of 3 doses of quadrivalent HPV vaccine, receipt of 1 or 2 vaccine doses was also associated with a considerable reduction in condyloma risk. No GWs occurred among vaccinated girls in the youngest birth cohort. The study in Denmark27 that included girls and women	The study in Uganda37 reported that ratio of HPV16 and HPV18 GMTs comparing 2 dose to 3 dose groups were 0.51 (97.5%CI=0.37-0.69), and 0.69 (97.5%CI=0.50-0.96).

Quadrivalent vaccine	Bivalent vaccine
from birth cohorts 1989–1999, which had a vaccine coverage rate (at least 1 dose) >10% reported that where age was taken into account, the relative risk of of GWs among vaccinated girls compared to unvaccinated girls was significantly decreased in vaccinated girls (i.e. having received at least 1 dose), and varied between 0.12 (95% confidence interval,04–.36, P< .001) in girls born during 1995–1996 and 0.62 (95% CI, .50–.76, P< .001) in girls born during 1989–1990, the trend of an increasing risk reduction with the younger birth cohort being statistically significant (P <.0001) The case control study in Australia[28] reported that the adjusted odds ratio for exposure to three doses of HPV vaccine compared with no vaccine was 0.54 (95% CI 0.43 to 0.67) for high grade cases and 0.66 (0.62 to 0.70) for other cases compared with controls with normal cytology, VE of 46% and 34%, respectively. The adjusted exposure odds ratios for two vaccine doses were 0.79 (95% confidence interval 0.64 to 0.98) for high grade cases and 0.79 (0.74 to 0.85) for other cases, VE of 21%.	

2-dose schedule versus 2-dose schedule: comparing different intervals between doses

Two RCTs using the bi-valent vaccine compared two 2-dose schedules with different intervals (Canada/Germany[29] [30] [31], 0, 2 vs. 0, 6 months) and Multinational2[41] [42] (0, 6 vs. 0, 12 months).

Results for Canada/Germany[29] [30] [31] indicated that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years). There are no data yet publically available from the Multinational2 study.

Summary of findings

2-dose schedule versus 3-dose schedules

- In randomised comparisons, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior or inconclusive compared with the 3-dose group. Seroconversion and seropositivity were non-inferior or inconclusive at alltime.
- In non-randomised comparisons, GMCs were non-inferior or superior in girls receiving the a 2-dose schedule compared with women receiving the 3-dose schedule at all time points assessed, up to 36 months after vaccination. All available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule.

- Limited data about clinical outcomes. The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of bivalent vaccine at month 48 indicates that the two-dose schedule prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course[4]. In the randomized comparisons, in one study, incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.
- Observational data overall support the findings from the trials. However, a number of considerations regarding these studies must be noted:
    - In the Australian observational linkage study (including attempts to reduce residual confounding) the vaccine effectiveness for two doses is estimated as less than for 3 doses for histological outcomes.
    - A stronger trend associated with age was observed. However, authors reported low evidence of effect until they control for age at vaccination and screening (an attempt to address issues associated with residual confounding).
    - There was a striking effect of vaccination associated with first screening (which in Australia takes place at 18 years of age). In addition, there were small numbers of girls 12-13 years of age receiving fewer doses, usually at a less than 4-6 months interval, and there are considerations to the effect that girls with incomplete immunization schedules maybe be different from those with 3-dose schedule.
    - In Sweden, an observational study using condyloma acuminata as the outcome of interest reported greater effect of greater number of doses. However, interpretations of results must include consideration to the so called *buffer period* (between vaccination and condyloma incidence – used as a proxy measure for prevalent HPV-infections) and interval between doses, which may result in an artifactual difference between 2 and 3 dose schedules. Data suggest that the differences between 2-dose schedule and 3-dose schedule were reduced, the *buffer* period was longer.

2-dose schedule versus 2-dose schedules: wider interval between doses

Two RCTs compared two 2-dose schedules with different intervals (0, 6 and 0, 12 months).

- Data from one of them reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years).

5. ROLE OF MATHEMATICAL MODELS TO INFORM IMPACT EVALUATION OF VARIOUS IMMUNIZATION SCHEDULES

The anticipated impact and cost-effectiveness of HPV vaccination has been extensively investigated in high-income countries, and this has provided the economic case for widespread vaccine adoption by majority of countries in the developed world. The findings of two models one from the United Kingdom (UK) and one from Canada were reviewed. Details of both models are summarized below.

UK model[44]	Canadian model (HPV-ADVISE)[45]
Compartmental transmission dynamic model of HPV infection, sexual transmission and natural history.	Individual-based transmission dynamic model of HPV infection, sexual transmission and natural history.
Models cervical neoplasia and cancers (squamous and glandular) due to HPV 16, 18 and other high risk types.	Models cervical neoplasia and cancers (squamous and glandular) due to HPV 16, 18 and other high risk types.
Used to inform UK vaccination policy.	Used to inform Canadian vaccination policy.

Both the UK and the Canadian model predicted that under the hypothetical assumption that a female-only two dose schedule has a duration of protection of at least 20 years, there will be few additional cases prevented by adding a third dose. However, if duration of protection is assumed to be below 10 years, then the additional benefit of the third dose is much greater.

Therefore, assumptions on the duration of protection are important. HPV vaccines have already demonstrated no waning of efficacy (for 3 doses) for almost ten years when given to young adolescent girls (through the peak years of HPV acquisition). If 2 doses provide long-lasting protection, as expected from the similar durability of antibody responses, we would expect them to behave in the same way.

The Canadian model further suggests that there will be little benefit in extending the target group to include boys.

Relative importance of HPV vaccine characteristics (in terms of population impact):

Duration of protection > cross-protection > initial efficacy (within 85%-100% range).

In high-income settings (such as the UK and Canada), if it is documented that a 2-dose vaccination confers more than 10-20 years protection then adding the third dose is not cost-effective. If it is documented that a 2-dose vaccination only provides up to 10 years protection, then adding the third dose may be cost-effective. The cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored.

6. IMPORTANT ISSUES FOR CONSIDERATION

HPV experts reviewed and discussed the available evidence during the WHO Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules organized in Geneva, November 18, 2013. In addition, the draft of this background document was circulated and comments were provided by the same experts via electronic mail in March 2014.

Below is a summary of the main points raised during these interactions.

[44] Jit et al. BMJ 2008; 337:a769; Choi et al. Vaccine 2010; 28:4091 and; Jit et al. BMJ 2011; 343:d5775
[45] www.hpv-advise.com; Van de Velde et al. Vaccine 2010; 28:5473 and; Brisson et al. Vaccine 2013

Progress and challenges with vaccine introduction

- There is disparity between the geographic distribution of the risk of HPV related cancer and the introduction of HPV vaccines, as most of the countries with the highest risk have not introduced the vaccine by November of 2013.
- Costs are among the main barriers for more widespread introduction of HPV vaccines.
- There are other implementation challenges with the introduction of HPV vaccines. Reaching high immunization coverage and estimating the HPV vaccine coverage achieved are both challenging. Some of the reasons for low coverage include the need to target various cohorts, the fact that current schedules require 3 doses to be administered within a 6 month period, the use of catch-up vaccination for introduction and the uncertainty of the denominator. Furthermore, tailored delivery strategies to reach all girls (including those not attending school), and special social communication strategies are required.

Use of immunogenicity data to inform policy recommendations on HPV schedules

- The available serological assays provide only a partial characterization of the immune status in vaccinated individuals. The observation that protection against HPV18 persists after antibodies become undetectable in some assays, as well as animal studies, suggests that the minimal antibody threshold required for protection is below the detection threshold of current assays. It is important to point out that the assay measuring HPV 18 antibody concentration measures only one antibody species, as when total anti-18 antibody is measured then seropositivity remains.
- Antibody concentration standard assay protocols are essential to compare various schedules in various settings. Antibody concentrations should be reported in International Units.
- The available immunogenicity data from bivalent vaccine indicates that both antibody quantity (titers) and quality (avidity) after a 2-dose (prime-boost) schedule in girls are non-inferior to responses after a 3-dose (prime-prime-boost) schedule in women: this is an informative element in risk assessment. It is important to emphasize the in vitro neutralizing titres since they encompass both elements of epitope specificity and avidity.
- The immunogenicity data for the quadrivalent vaccine leads to similar conclusions, but is currently more limited (in vitro neutralization, avidity).
- The induction and persistence at 12 months of non-inferior antibody titers after 2 prime-boost doses in the younger age group compared to adult women suggests that an alternate (0–6 months) and reduced dosing (2 instead of 3) schedule of HPV vaccination could be considered for the younger age group. These proposals, however, do not apply to immunocompromised individuals, because their vaccine responses may be less strong and there is no data with 2-dose schedules from these groups.
- There is limited immunogenicity data for a 0-6 or 0-12 schedule in less than 13 year old females.
- Decision makers need to assess the degree of risk and benefits of various schedules and their ability to implement effective surveillance post immunization and devise risk management strategies in the event of a worst case scenario after 2 or 3 initial doses (e.g. if longer term data indicate the need for additional doses of vaccine).

Evidence on the effect of fewer than 3 doses of HPV vaccine

- The interpretation of clinical trials or observational studies reporting vaccine efficacy after 2 versus 3 doses should take into account the immunological evidence suggesting that a 2-dose schedule must include at least 4 months before the 2nd dose to fulfill the criteria of a prime-boost (and not a prime-prime) schedule.
- Limited data on efficacy and effectiveness with limited follow –up (e.g. up to 4 years) support these findings. The bivalent vaccine has obtained EMA approval for a 2-dose schedule and the quadrivalent vaccine has already obtained a positive opinion of the CHMP. Longer term studies are underway.
- In countries where sufficient immunization coverage will be achieved in the target age groups, the strong herd immunity elicited by HPV vaccines is expected to make a large contribution to protection, reducing the likelihood of the need for late boosters.
- There are limited data on 3-dose schedules[46] in HIV infected populations and no data were identified on schedules using fewer than 3 doses in these populations. As cervical cancer is an AIDS-defining illness, recommendations about a 2-dose schedule might differ for populations with low and high HIV prevalence rates. However, 1) the limited data available indicate that HPV VLPs are strongly immunogenic even in HIV-infected women and 2) this concern might be mitigated if immunizing young adolescent girls prior to the onset of sexual activity to elicit strong and sustained HPV immunity prior to HIV acquisition and subsequent immunosuppression.

Role of mathematical models to inform impact evaluation of various immunization schedules

Models can be useful to inform choice of immunization policies and to estimate cost effectiveness at country and regional level. Information on the duration of protection of various schedules is important. As there are fewer data on duration of protection for the 2-dose schedule, additional data would be informative.

The anticipated impact and cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored. In particular it would be informative to explore various implementation scenarios and coverage assumptions and assess their anticipated impact. Moreover, model explorations would help to highlight data needed to inform key variables and assumptions such as the duration of protection and the herd immunity thresholds in various settings.

[46] For example, Quebec, Canada guidelines propose 3 doses, but extended (0, 6, 12) to immunosuppressed pre-adolescents. http://publications.msss.gouv.qc.ca/acrobat/f/documentation/piq/piq_complet.pdf

7. RECOMMENDATIONS FOR SAGE's CONSIDERATION

There are obvious programmatic advantages to reducing the number of doses (e.g. reduced delivery costs), and flexible intervals between doses (e.g. annual doses easier for school-based delivery) might also lead to increase in vaccination coverage.

The 2009 WHO position paper states that the first dose should optimally be given at 9-13 years of age as data suggest that HPV vaccines are most efficacious in girls who are naïve to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity[6].

Number of doses	
Recommendation	**Two dose (prime-boost) schedules (including at least 6 months between the first and the 2nd dose) are expected to provide similar protective efficacy compared to 3 dose schedules.** • A 2-dose schedule may be recommended to adolescent girls 9-13 years of age. • For girls primed before the age of 14 years, even if older at time of boosting (second dose), a 2-dose schedule may be considered.
Summary statement	The available evidence, and the understanding of HPV vaccine-mediated protection, indicates that two doses of HPV vaccine in girls 9-14 years of age are non-inferior to 3 doses in terms of immunogenicity when compared to 3 doses in girls 9-14 years or 3 doses in older women 15-24 years of age. The magnitude of the vaccine response is determined by the age at the first dose. Data indicate that following a 2-dose prime-boost schedule antibody titers in girls 9-14 years of age are mostly non-inferior to 3-dose titers in girls and are non-inferior to those in older young women. The inference is that a 2-dose vaccine schedule will be as efficacious as 3 doses, even though clinical efficacy data in girls are not available. Data on efficacy and effectiveness with limited follow–up (e.g. up to 4 years) support these findings. The bivalent vaccine has obtained EMA approval for a 2-dose schedule and the quadrivalent vaccine has already obtained a positive opinion of the CHMP.
Caution	There are fewer data comparing the efficacy of 2 versus 3 dose schedules. Longer term studies are underway. No data on fewer than 3 doses among HIV infected and immune-compromised populations are available.

Interval between doses	
Recommendation	**For 2-dose schedules, the minimal interval between doses should be 6 months.** The interval between the first and second dose may be extended up to 12 months should this facilitate administration – for example in school settings.
Summary statement	A second dose of vaccine given $\geq$ 6 months after the first dose (prime-boost) elicits an immune response non-inferior to that of a 3-dose schedule that uses a prime-prime boost approach. Data from one RCT reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years). Results from a multi-centric study would be available in the mid-term.
Caution	Data available is from one RCT

Special populations	
Recommendation	**The recommendation to target very young (9-10 year old girls) prior to sexual debut and risk of HIV acquisition is especially important in areas where HIV is prevalent.** o A 3-dose schedule should be offered to individuals known to be immunocompromised at time of immunization
Summary statement	Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer.
Caution	There are limited data from HIV-infected individuals receiving a 3-dose schedule and, no data from HIV-infected individuals receiving a 2-dose schedule.

8. RESEARCH PRIORITIES

Although some additional evidence is desirable, the participants concluded that these research priorities should not delay the development of recommendations related to a 2-dose schedule for HPV vaccine. The following research questions that could help inform future policy recommendations were outlined:

- It is very important to ensure the follow up of the cohorts under study in India and to duplicate similar studies in other settings, especially in LMICs.
- Definition of end points for second generation vaccines (e.g. immunogenicity end points) would provide additional guidance for the evaluation of alternative immunization schedules including 2- or 1-dose schedules with different intervals between doses (e.g. extended schedules) and in different epidemiological settings.
- Given that the two currently licensed vaccines are different and use different adjuvants, there is value in conducting head to head comparisons of various alternative schedules.
- Longer-term clinical effectiveness studies are needed to formally define the duration of protection after a 3-dose schedule, and whether a booster may be needed at some point given that immune memory is unlikely to be reactivated by exposure. This also applies to 2-dose schedules. High efficacy over time is needed because women continue to be at risk for infection, and the period of risk may vary from one culture to another.
- Studies must be done in regions where high rates of vaccination have not yet occurred because of high herd protection conferred by the 3-dose regimen.
- Multicenter studies in low income countries among healthy adolescent girls and among special populations (e.g. HIV-infected, malnourished adolescents, endemic malaria infection) would also provide additional evidence.
- The impact of various HPV vaccination schedules among HIV-infected individuals is important. Perhaps all available data – also limited- should be systematically reviewed and assessed.
- The anticipated impact of cost-effectiveness of 2-dose vs. 3-dose vaccination in low/middle income settings still needs to be explored. Additional model and economic evaluations that consider alternative scenarios of low coverage and various assumptions on effectiveness and duration of protection in LMICs are important.
- The group noted that the US National Cancer Institute (NCI) is considering an RCT to assess the effect on persistence of DNA and immunogenicity of HPV vaccines after 1 or 2 doses in an area with low to moderate vaccine uptake.

9. Appendices

Appendix 1. HPV vaccines: systematic review of alternative vaccination schedules

Appendix 2. HPV vaccines: non-systematic review of the data from observational studies

10. Annexes

Annex 1
List of Participants and Agenda of the Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules organized in Geneva, November 18, 2013

List of Participants
Sir Andrew Hall (Chairperson)

Julia Brotherton – Victorian Cytology Service (via Webex)
Maddalena D'Addario – University of Bern
Lisen Arnheim Dahlstrom – Karolinska Institutet
Simon Dobson - BC Children's Hospital
Dorota Gertig – Victorian Cytology Service (via Webex)
Vladimir Gilca – Institut national de santé public du Québec
Mark Jit – Public Health England
Eduardo Lazcano-Ponce – Mexico Institute of Public Health
Amy Leval – Karolinska Institutet
Lauri Markowitz – CDC
Rengaswamy Sankaranarayanan – IARC
Chantal Sauvageau - Institut national de santé public du Québec
John Schiller – NIH/NIAID
Claire-Anne Siegrist – Centre Médical Universitaire
Margaret Stanley – University of Cambridge

Industry representatives
Attila Mihalyi – GSK
Alfred Saah - Merck

WHO Secretariat
Paul Bloem, EPI/IVB
Philippe Duclos, DO IVB
Tracy Goodman, EPI/IVB
Sami Gottlieb, RHR
Ana Maria Henao-Restrepo DO/IVB
Olivier Lapujade, HIS/EMP
Drew Meek, HIS/EMP/PQT
Ximena Riveros, IVR/IVB
Susan Wang, EPI/IVB

Appendix 1

UNIVERSITÄT BERN

HPV vaccines: systematic review of literature on alternative vaccination schedules

Report on a two doses vs. three doses schedule

3rd March 2014

Maddalena D'Addario, Pippa Scott, Shelagh Redmond, Nicola Low

Institute of Social and Preventive Medicine (ISPM),

University of Bern,

Bern, Switzerland

Contents

Summary

This report summarises data to inform the discussion about optimal schedules for HPV vaccines for adolescent girls living in different epidemiological settings.

The included studies were identified in a systematic review and cover available immunological and clinical outcomes for comparisons of: 2-dose schedules in adolescent girls (the target group for primary HPV vaccination) versus 3-dose schedules in adolescent girls or women; and 2-dose schedules versus alternative 2-dose schedules.

2-dose schedule versus 3-dose schedules

Comparisons between 2-dose HPV vaccination schedules in girls in the target age group and the licensed 3-dose schedule cannot be randomised if the comparison group is women in the age group amongst whom clinical efficacy was established. The least biased comparisons are controlled trials that enrol girls and women concurrently using the same clinical trial protocol. Randomised comparisons are possible between girls (or women) of the same age who are enrolled and allocated at random to a 2-dose or 3-dose schedule.

We identified three randomised controlled trials (RCTs, Canada1 (quadrivalent), Canada/Germany1 (bivalent), India (quadrivalent)) comparing a 2-dose (0, 6 months) with a 3-dose (0, 1 or 2, 6 months) schedule in girls and four non-randomised controlled trials (Canada1, Canada/Germany1, Mexico (bivalent), Multinational2 (bivalent)) comparing a 2-dose schedule in girls with a 3-dose schedule in women.

In randomised comparisons, 1 month after the last dose, geometric mean concentrations (GMCs) in the 2-dose group were lower but non-inferior or inconclusive compared with the 3-dose group in Canada1 and Canada/Germany1. In India the ratio of antibody levels was higher in the 2-dose group. At 24 months, results from Canada1 and Canada/Germany1 were lower in the 2-dose group and the lower 95% confidence interval included the non-inferiority margin. Seroconversion and seropositivity, assessed in Canada1 and Canada/Germany1 were non-inferior at all time points assessed except at 24 and 36 months in Canada1, when they were inconclusive. The RCT in India provided limited data about clinical outcomes: incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.

In non-randomised comparisons, GMCs were non-inferior or superior in girls receiving the 2-dose schedule compared with women receiving the 3-dose schedule in all four trials at all time points assessed, up to 24 months after vaccination. All available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule. There were no clinical outcome data available for these four controlled trials.

2-dose schedule versus 2-dose schedules

Two-dose schedules can vary according to the interval between doses or the dosage of vaccine subtypes. Schedules can be evaluated in RCTs in girls in the target age group for HPV vaccination.

We identified two RCTs comparing two 2-dose schedules with different intervals (Canada/Germany1, 0, 2 vs. 0, 6 months) and Multinational2 (0,6 vs. 0,12 months). Results are only available for Canada/Germany1. The 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years).

We found one trial (Canada/Germany1) that compared different dosages of HPV (40µg vs. 20µg) given in a 2-dose schedule (0, 6 months). The higher dosage elicited higher GMCs.

1 Introduction

1.1 Background to comparisons of 2-dose and 3-dose HPV vaccine schedules

HPV vaccine has been licensed in >100 countries around the world. High levels of vaccine uptake have been achieved in some countries, e.g. Australia, but uptake has been sub-optimal in many countries. There are fewer organised opportunities for vaccinating adolescents, especially where secondary school attendance is low. Vaccination schedules would be simpler and cheaper if fewer doses could be used to achieve the same clinical effect.

Two HPV vaccines are licensed for use in adolescent girls, a bivalent vaccine containing purified L1 proteins (referring to the late protein expression region of the genome) from HPV types 16 and 18 (Cervarix, GlaxoSmithKline) and a quadrivalent vaccine containing purified L1 proteins from HPV types 6, 11, 16 and 18 (Gardasil, Merck).

The randomised trials (RCTs) that were done to obtain licensure compared 3 doses of HPV vaccine with placebo in 16-26 year old women. Pre-coital adolescent girls could not be enrolled for ethical and practical reasons. Both vaccines showed high levels of protection against cervical intraepithelial neoplasia grade two or above.

The license for use in adolescent girls was obtained through bridging studies showing that antibody responses in adolescent girls receiving the same 3-dose schedule were non-inferior to those in 16-26 year old women (Figure 1).

There are some interesting challenges involved in comparing the effects of 2-dose and 3-dose HPV vaccine schedules:

a. The published clinical efficacy data about cervical intraepithelial neoplasia from RCTs are in women, but the main target population for vaccination is 9-14 year old girls;
b. These groups cannot be compared in RCTs because you cannot allocate people to different age groups;
c. There might be age-related immunological differences in the initial response to HPV vaccine and to the persistence of immune responses over time;
d. The published data to date are for immunological outcomes and there are no publicly available data from RCTs about the clinical efficacy of 2-dose schedules in adolescents.

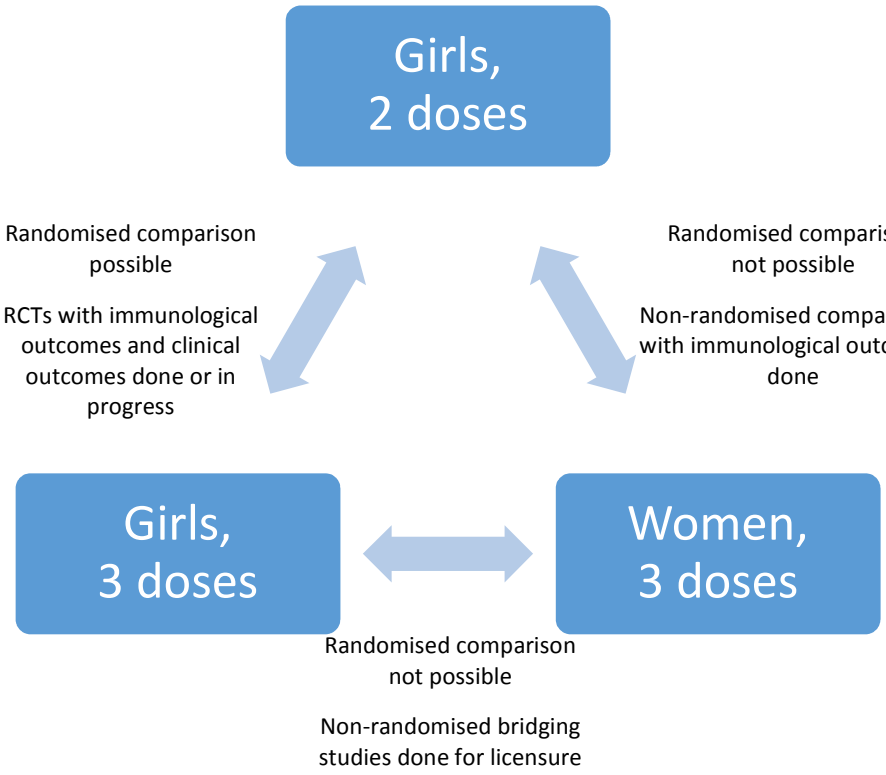

Figure 1: Desired and available comparisons between schedules and target populations

Girls, includes pre-coital girls and adolescents, generally aged 9 to 14 years; women, includes pre- or post-coital women, generally aged 16 to 26 years

1.1.1 Description and terminology used for comparisons between two and three doses of HPV vaccine

We describe two main types of comparisons between schedules for which we present data about the effects of two doses and three doses of HPV vaccine:

a. **Randomised comparisons within girls of the same age group of a study population that has been randomly allocated to receive different schedules of HPV vaccine;**

b. **Non-randomised comparisons between different age groups that have received different schedules of HPV vaccine in girls and women enrolled using the same study protocol and, according to age, allocated to receive two or three doses.**

Additional evidence can be derived from studies with other study populations or other designs. The risk of bias is higher for non-randomised comparisons within the same age group than for randomised comparisons:

c. **Randomised comparisons within women of the same age group of a study population that has been randomly allocated to receive different schedules of HPV vaccine;**

d. **Non-randomised comparisons within the same age group of a study population in which participants**
   i. Were randomly allocated to a 3-dose vaccination schedule but some received only two doses;
   ii. Were not randomly allocated and participants received different numbers of vaccine doses, e.g. non-randomised controlled clinical trial or observational study within a demonstration project;

1.1.2 Immunological outcomes of HPV vaccination

HPV vaccine induces high levels of antibody against type-specific HPV L1 virus like proteins, which protect against clinical disease in women without evidence of previous exposure to a specific HPV type [1]. Seroconversion from antibody negative to antibody positive (any detectable antibody) status occurs in almost all vaccinated individuals. There is currently no immune correlate of protection.

Laboratory tests to measure antibody concentrations differ for the two HPV vaccines [1]. This makes it difficult to compare absolute levels of antibody between studies that have used different vaccines.

Immunological responses can be presented as:

- Absolute levels of antibodies (usually presented as geometric mean antibody concentrations, GMCs)
- A percentage of the study population with antibodies above a given threshold which, for HPV is an antibody concentration greater than the assay threshold for a specific HPV type. The percentage with antibodies can be presented as:
    - The overall percentage seropositive
    - The percentage with evidence of seroconversion, i.e. post-vaccination seropositivity amongst individuals without detectable antibody before vaccination.

For trials of HPV vaccines, the percentages seropositive and seroconverting are often the same because analysis in RCTs is often restricted to participants who have no serological evidence of pervious exposure to HPV.

In published studies, data are more often presented as GMCs than as percentages seroconverting or seropositive after vaccination.

Non-inferiority between immunological responses with two and three doses

Given that the licensed 3-dose HPV vaccination schedule is highly efficacious in preventing pre-cancerous cervical lesions caused by HPV 16 and 18, the evidence about 2-dose vaccination schedules needs to come from trials designed to show non-inferiority. Non-inferiority means that a new treatment (e.g. a 2-dose schedule) is no worse than the existing treatment (3-dose schedule), by more than a pre-determined amount [2]. A standard approach is to hypothesise that there is no real difference between the two vaccination schedules. The confidence intervals of the observed absolute difference are then used to decide whether the new treatment is non-inferior.

Figure 2 shows different possible scenarios in trials and how the confidence intervals for the observed difference are interpreted in a non-inferiority trial. We based the figure on one presented by the authors of the CONSORT (Consolidated Standards of Reporting in Trials) Statement on the

reporting of non-inferiority trials [2]. The orientation of the figure corresponds to the convention that we used in this review; 2-dose (new treatment) *minus* 3-dose (conventional treatment).

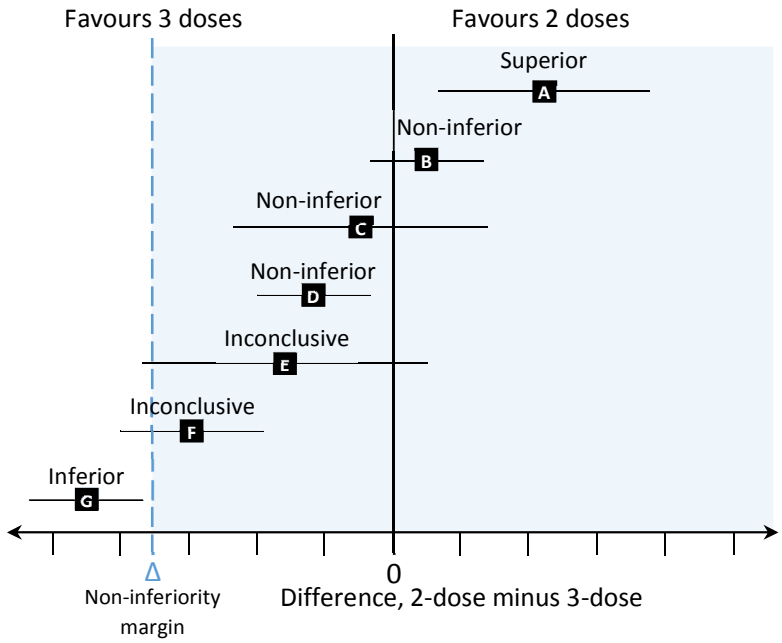

Figure 2. Interpretation of differences between 2-dose and 3-dose schedules of HPV vaccines in non-inferiority trials

Generic forest plot. Boxes indicate point estimates of effect size, error bars are 95% CI. Solid black line is null effect. Blue dashed line is the non-inferiority margin at Δ (difference between 2-dose and 3-dose schedule). Scenario A, 2-dose schedule is superior to 3-dose schedule; scenarios B, C, D, 2-dose HPV schedule is non-inferior to the standard 3-dose schedule because the lower 95% CI is to the right of the non-inferiority margin; scenarios E and F are inconclusive because the lower 95% CI includes the non-inferiority margin; scenario G, 2-dose schedule is inferior to the 3-dose schedule. Based on Piaggio G et al. [2].

2 Review methods

This report covers all evidence deriving from the systematic review of literature on comparisons 1 as described below in order to answer the review question. . The systematic review concerning comparison 2 and 3 is still in progress . We state in the methods and results sections tasks that have yet to be completed.

Here we report on comparison 1 and present tables in the Appendix showing trials identified so far for all three comparisons.

2.1 Objective

The objective of this study is to systematically review trials comparing the effects of 2-dose and 3-dose HPV vaccination schedules.

2.1.1 Review question

What is the effect of 2 doses of HPV vaccine compared with the licensed 3-dose schedule on immunological and clinical outcomes in adolescent girls?

2.1.2 Population, Intervention, Comparisons, Outcomes, Study design (PICOS)

Population: Adolescent girls aged 9 to 14 years (priority age group because this is the target group for primary vaccination)

Intervention: licensed bivalent (Cervarix, GlaxoSmithKline) or quadrivalent (Gardasil, Merck) HPV vaccine

Comparison:

1. Two doses vs. three doses of the same vaccine and the same dosage (3-dose arm using the WHO recommended schedule);

2. Two doses vs. two doses comparing schedules with different intervals (same vaccine and same dosage) or different dosage (where one comparator arm uses the licensed dosage);

3. Three doses vs. three doses (with one arm using the WHO recommended schedule) comparing schedules with different intervals (or different dosage where one comparator arm is the licensed concentration) (to be done if time allows).

Outcomes:

1. Immunological (including, but not limited to GMC, seropositivity, seroconversion, avidity);

2. Clinical (including, but not limited to CIN3+, CIN2+, genital warts, incident infection).

Study design: Randomised controlled trials (RCTs) examining comparisons 1-3; for comparison 1, non-randomised prospective controlled trials comparing two doses in girls with three doses in women. For all comparisons, we will document studies using other designs that might provide additional evidence.

2.1.3 Search strategy

We searched the US National Library of Medicine electronic database (PubMed), the Cochrane Central Registry of Controlled Trials (CENTRAL) and trials register from their earliest publication date to the last week of January 2014. We also searched abstracts from the 2013 meeting of the European Research Organisation on Genital Infection and Neoplasia (EUROGIN), regulatory dossiers provided by representatives of the vaccine companies GlaxoSmithKline and Merck, and studies presented at a WHO ad hoc meeting in November 2013.

The search terms were chosen to optimise sensitivity for the identification of RCTs. Comparisons between girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule are non-randomised. We assessed this non-randomised comparison in items retrieved from the searches, studies cited in reference lists or mentioned by experts and studies reported in manufacturers' dossiers. This strategy might, however, have missed eligible studies.

2.1.4 Study selection

One reviewer conducted the search, de-duplicated titles and screened titles for potential eligibility, excluding those that did not fit any inclusion criteria. Two reviewers then independently screened titles and abstracts of the remaining items to select potentially eligible articles. Two independent reviewers read the full text of potentially eligible articles to decide on their inclusion.

2.1.5 Study organisation and terminology

We refer to studies first by the countries in which participants were enrolled, and then by the valency of the vaccine. When more than one study has been done in the same country we number them 1, 2, 3, etc. Many studies have more than one document associated with them, including trial registry listings, manufacturers' clinical trial reports, conference abstracts and meeting presentations and journal publications. We grouped together all documents associated with the same trial and refer to the trial by its study name. The first time a study is mentioned in the results, we give the study name and citations to all its associated documents.

We also stratify results by geographical setting, with high income countries in one stratum and low- and middle-income countries in another, based on World Bank thresholds for per capita income. We grouped one multinational RCT with participants from Canada, Germany, Italy, Taiwan and Thailand in the high income stratum; more than half of participants were from high income countries in Europe (53.4%), Taiwan (20.7% of participants) is not considered as a separate country but its income level is above the threshold for high income countries and Thailand (23.8% of participants) is an upper middle income country.

2.1.6 Data extraction

One reviewer extracts data into a structured form created in Epidata (Odensk, Denmark). A second reviewer checks the extracted data. The reviewers discussed discrepancies and make corrections if necessary.

We used data described in the text as well as in tables. If authors gave approximate numbers for near complete seroconversion/seropositivity, we assigned values of 100%. For example, in the trial Canada1, for HPV16, the study report says, “The majority of participants (>99%) remained seropositive for HPV-16…” [3].

2.1.7 Data analysis

We used Stata version 13 (StataCorp, Austin, USA) for analysis to prepare forest plots and, where appropriate, conduct meta-analysis.

We have used data from per-protocol populations, where available, because most comparisons were made to investigate non-inferiority of one vaccination schedule compared with another and the per protocol study population gives a more conservative estimate of the difference between two schedules.

For analyses of the proportion of participants with any antibody detected after vaccination we use, where stated, participants who were seronegative at baseline. This gives the proportion that seroconverts after vaccination. For longer follow up times we then report the proportion remaining seropositive. If seropositivity data were not stratified by pre-vaccination status we used the whole study population.

Outcome measures

We compare available data about serological antibody responses measured as GMCs or seroconversion/seropositivity. We present the following:

a. GMCs: for HPV16 and HPV18 separately, weighted mean difference (95% CI) between GMCs, calculated as i) girls receiving two doses *divided by* girls receiving 3 doses and ii) girls receiving 2 doses *divided by* women receiving three doses. The weighted mean difference on the log scale is the number needed if meta-analysis is planned because precision is expressed in terms of the log standard error. The point estimate and lower and upper confidence intervals can be exponentiated to give the ratio of GMCs and its confidence intervals. These are comparable to published data presented as a GMC ratio. For non-inferiority, we use the non-inferiority margin cited by Dobson et al. as “the lower bounds… for a GMT ratio… greater than 0.5” [3]. On the log scale this is -0.693.
b. Seroconversion/seropositivity: for HPV16 and HPV18 separately, difference (with 95% confidence intervals, 95% CI) between percentage seroconverted/seropositive, calculated as i) girls receiving two doses *minus* girls receiving three doses and ii) girls receiving two doses *minus* women receiving three doses. If a non-inferiority margin of 5% is set, the lower 95% confidence interval for the difference should be above -5%.

We do not compare absolute levels of antibody concentrations because of the different methods used to measure them. We have assumed that it is valid to compare: a) the log difference, which corresponds to a ratio of GMCs on the natural scale; and b) the difference in percentages seropositive after vaccination. We examine heterogeneity between results of different studies visually in forest plots and quantitatively using the I^2 value. If meta-analysis is appropriate, we use a random effects model to estimate the weighted average of the pooled effects.

2.1.1 Search results

The search strategies yielded a total of 923 hits. (Figure 3).

Table 5 (in the appendix) summarises the main characteristics of identified RCTs, including the schedules compared.

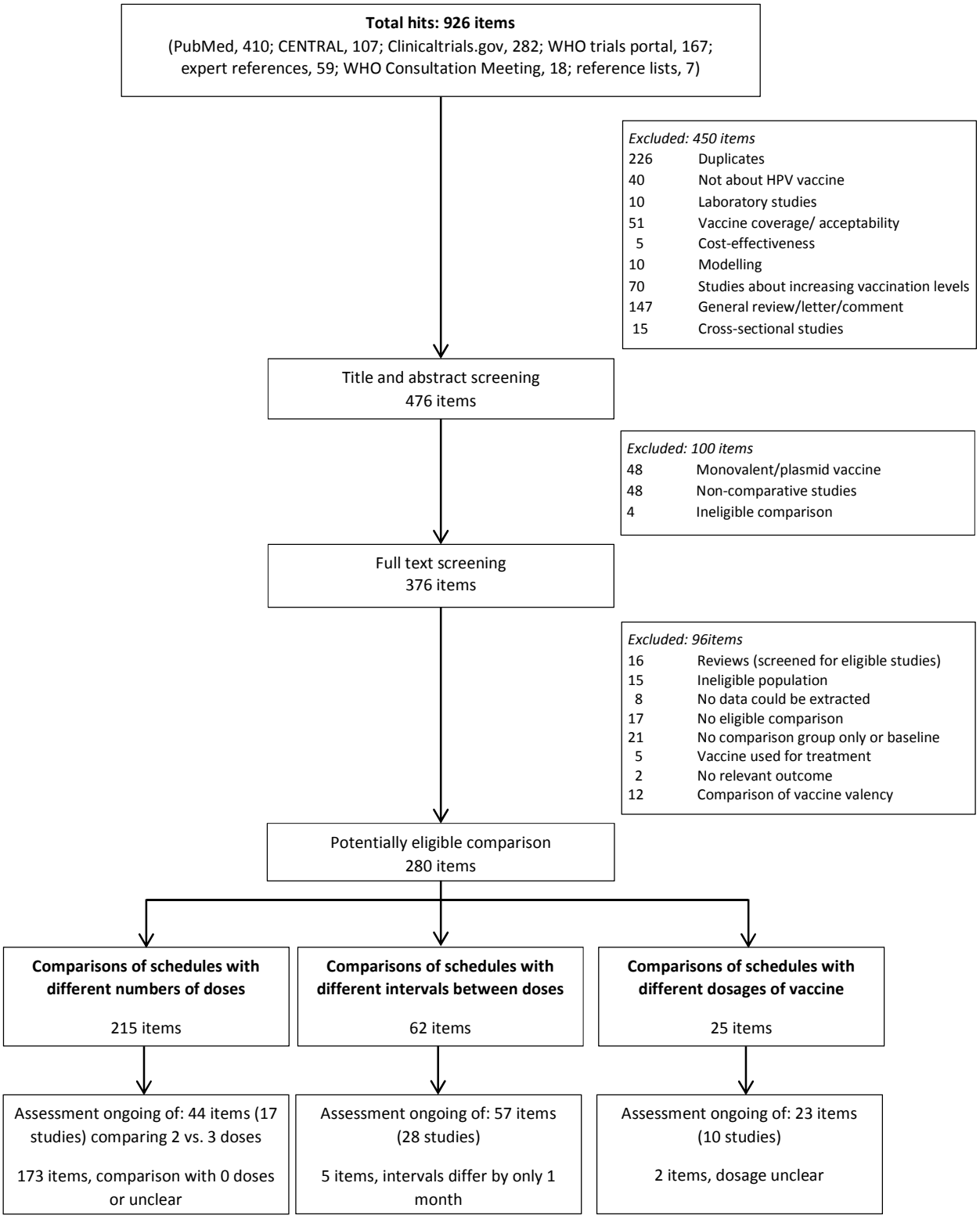

Figure 3. Flow chart of retrieved items, excluded and included items, and number of studies according to comparison, as of 28.02.2014.

3 Comparison 1: two doses vs. three doses of the same vaccine and the same dosage (3-dose arm using the WHO recommended schedule)

We summarise the studies identified in the search strategy as of 01.03.2014. We then present results for randomised comparisons in girls, followed by non-randomised comparisons between girls and women and then we summarise results from studies with other designs or populations. Within each group of studies we present available results for GMC, seroconversion/seropositivity, and clinical outcomes.

3.1 Studies identified

Table 1 summarises the comparisons made in this section of the report for primary evidence about the effects of 2-dose vs. 3-dose HPV vaccine schedules and forest plots showing the results. Table 2 shows the basic characteristics of all identified studies comparing 2-dose and 3-dose schedules.

Table 1. Comparisons made with data available for primary sources of evidence

Study name	Girls, randomised comparisons					Girls vs. women, non-randomised comparisons				
	GMC		Seroconversion/ positivity		Clinical	GMC		Seroconversion/ positivity		Clinical
	1 month	later	1 month	later		1 month	later	1 month	later	
Canada1	+	+ (24, 36)	+	+ (24, 36)	-	+	+ (24, 36)	+	+ (24, 36)	-
Canada/Germany1	+	+ (24)	+	+ (24)	-	+	+ (24)	+	+ (24)	-
India	+	-	-	-	+	-	-	-	-	-
Mexico	-	-	-	-	-	+	+ (21)	+	+ (21)	-
Multinational2	-	-	-	-	-	+	-	+	-	-
Figure	Figure 4,	Figure 5,	Figure 6		None	Figure 7	Figure 8	Figure 9		None

We included three RCTs that compared a 2-dose and 3-dose schedule in girls between 9 and 18 years old: Canada1 [3-5]; Canada/Germany1 [6-8]; and India [9, 10], all of which provide data about antibody concentrations at month seven (one month after the last vaccine dose). All three trials have been designed to investigate differences in immunological outcomes. There are limited data about the methods of the India trial, which does not yet have published results. The authors present the ratio between antibody concentrations as the mean fluorescence index (MFI). We assumed that this corresponds to the geometric mean antibody concentration used in other trials. The India trial has also been designed to investigate clinical outcomes, with planned follow up of more than 20 years. The authors will use blood samples to assess incident HPV infections and cervical cell collection starting after marriage or the first delivery.

One additional RCT provides data for women aged 15-25 years [11]. This trial in Europe (Italy, Romania, Slovakia) compared two 3-dose schedules (extended: 0, 1, 12 months vs. standard: 0, 1, 6 months). For the extended schedule, data are available at month two (one month after the second dose) and compared with month seven (one month after the third dose of the standard schedule).

Table 2. Summary of identified studies reporting on comparisons between two and three doses of HPV vaccine, by study design, study name and population

Study name [refs], (vaccine)	Alternative study names	Study design details relevant to 2-dose vs. standard 3-dose comparison	Schedules, months*	Comparisons presented of 2-dose vs. 3-dose schedules
Primary evidence, controlled trials				
Canada1 [3-5, 12], (quadrivalent)	BCGov01	RCT, non-inferiority: girls (9-13 yrs) allocated to 2-dose or 3-dose schedule; women (16-26 yrs) enrolled concurrently and given 3-dose schedule	0, 6 0, 2, 6	Randomised, girls Non-randomised, girls vs. women Immunogenicity
Canada/Germany1 [6-8, 13], (bivalent)	HPV-048	RCT, non-inferiority, dose-range: girls (9-14 yrs); women (15-19, 20-25 yrs) allocated to 2-dose or 3-dose schedule (and, within 2-dose schedule)	0, 6 0, 1, 6	Randomised, girls Non-randomised, girls vs. women Randomised, women Immunogenicity
India [9, 10], (quadrivalent)	NCT00923702 BMGF48979	RCT: girls (10-18 yrs) allocated to 2-dose or 3-dose schedule (unpublished, methods from trial registration and meeting report)	0, 6 0, 2, 6	Randomised, girls Immunogenicity, clinical
Mexico [14], (bivalent)		Controlled trial: 81 schools in two clusters allocated to two 3-dose schedules; girls (9-10 yrs) receive vaccine; concurrent enrolment of women (18-24 yrs) to receive 3-dose schedule. Compared after extended schedule group receives two doses. No account taken of clustering.	0, 6 (60) (extended) 0, 1, 6	Non-randomised, girls vs. women Non-randomised, girls Immunogenicity
Multinational2 [13, 15, 16] (Canada, German, Italy, Taiwan, Thailand), (bivalent)	HPV-070; GSK 11470; GSK580299	RCT, non-inferiority: girls (9-14 yrs) allocated to two 2-dose schedules; concurrent enrolment of women (15-25 yrs) to 3-dose schedule.	0, 6 (0, 12) 0, 1, 6	Non-randomised, girls vs. women Immunogenicity
Additional supporting evidence				
Canada2 [17-19]	ICI-VPH; NCT02009800	RCT, non-inferiority girls who received 2 doses (at age 9-11) 5 years before enrolment allocated to 3rd dose or not	0,6 0,6,60	No results yet Randomised, girls Immunogenicity, clinical
Europe [11] (Italy, Romania, Slovakia) (bivalent)	NCT00552279	RCT, non-inferiority: women (15-25 yrs) allocated to two 3-dose schedules. Compared after extended schedule group receives two doses.	0, 1 (12) (extended) 0, 1, 6	Randomised, women Immunogenicity
Costa Rica [5, 13, 20-23], (bivalent)	HPV-009	RCT, efficacy: women (18-25 yrs) allocated to 3-dose schedule or 0 doses. Compared fully (three doses) with partially vaccinated (two doses).	0, 1, 6 (0)	Non-randomised, women Immunogenicity, clinical
Multinationalx [13, 24], 14 countries, (bivalent)	HPV-008; PATRICIA	RCT, efficacy: women (15-25 yrs) allocated to 3-dose schedule or 0 doses. Compared fully (three doses) with partially vaccinated (two doses).	0, 1, 6 (0)	Non-randomised, women Clinical
Multinational4 [25, 26] (France, Hong Kong, Singapore, Sweden) (bivalent, quadrivalent)	HPV-071 PRI GSK 11541; NCT01462357	RCT, girls (9-14 yrs) allocated to 2 vs 3 doses quadrivalent or 2 doses bivalent	0, 6 (0, 6) 0, 2, 6	No results yet Randomised, girls Immunogenicity
Uganda [27], (vaccine not	PATH	Observational study, demonstration project: girls invited to receive 3-dose schedule. Compared fully (three doses)	0, 1, 6	Non-randomised, girls Immunogenicity

stated)		with partially vaccinated (two doses).		
Canada3 [18, 28-30] , (quadrivalent)		RCT, co-administration and alternative third dose: girls allocated to concurrent or sequential hepatitis A vaccine. After two doses allocated to third dose bivalent or quadrivalent. Compared same girls after two and three doses.	0, 6, 42	Within-person, girls
Canada4, (quadrivalent) [3, 31]	QUEST	Observational study, longitudinal cohorts of girls (9-12) who received 2 or 3 doses followed up until age 19 or 10 years after 1st dose	0,6 0,2,6	No results yet Non-randomised, girls Immunogenicity, clinical

* Vaccine doses in brackets are in study protocol but data not used in this report.

We included four studies with concurrent enrolment of girls and women that provide data about non-randomised comparisons between a 2-dose schedule in girls and a 3-dose schedule in women: three were comparisons within RCTs, Canada1 [3-5]; Canada/Germany1 [6-8], Multinational2 (Canada, Germany, Italy, Taiwan and Thailand) [15, 16]. One non-randomised controlled trial was included in this group (Mexico) [14]. This trial, in Cuernavaca, enrolled women from a primary health care centre and girls from schools. Girls were grouped into "2 clusters, each of which included students from a different set of local public schools." Girls in one group of schools received an extended schedule of bivalent vaccine (0, 6, 60 months) and provided a blood sample at months seven and 21, which could be compared with results from women at the same intervals after the standard 3-dose schedule. Of note, the authors do not mention any adjustment for clustering when calculating confidence intervals for estimates from girls.

We also identified four additional studies presenting non-randomised comparisons between groups of the same age receiving two or three doses of HPV vaccine. Two RCTs of clinical efficacy in Costa Rica [13, 22] and in 14 different countries [13, 24] compared partially and fully vaccinated women; one non-randomised controlled trial allocated girls two clusters of schools in Mexico non-randomly to different schedules [14]; and one demonstration project in Uganda compared partially and fully vaccinated girls [27].

3.2 Randomised comparisons in girls

Three RCTs (Canada1, Canada/Germany1 and India) contribute to these comparisons. All three present immunological outcomes as GMCs. Canada1 and Canada/Germany1 also present these data as seroconversion (percentages of girls initially seronegative who are seropositive after vaccination. India presents limited clinical outcomes about incident HPV infections. The numerical data extracted from these RCTs are summarised in Table 6 (appended).

3.2.1 Geometric mean antibody concentrations

Figure 4 shows the difference in GMCs between girls receiving two or three doses of HPV vaccine one month after the last vaccine dose.

For HPV16, the trials have inconsistent results (I^2 93%).

- The 2-dose schedule in the Canada1 trial is non-inferior to the 3-dose schedule.
- In Canada/Germany1, the GMC is lower in the 2-dose than the 3- dose group. The lower bound of the confidence interval is below that non-inferiority margin but the upper bound is above it so the result is inconclusive.

For HPV18 the results of the trials are consistent and the GMC in the 2-dose group is non-inferior to that in the 3-dose group (the weighted mean difference corresponds to a GMC ratio of 0.72, 95% CI 0.62, 0.84).

Limited data from the India trial were presented at the WHO *ad hoc* meeting in November 2013. In the India trial, comparisons favoured the 2-dose schedule. The weighted mean differences correspond to a mean fluorescence index for HPV16 of 1.2 (1.0, 1.2) and for HPV18 1.0 (1.0, 1.2).

Figure 5 shows the results at 24 months for both studies. Point estimates for the weighted mean difference are lower for the 2-dose group in both trials for both HPV16 and 18. Lower bounds for the confidence interval are below the non-inferiority margin for HPV18 in both trials and for HPV16 in Canada/Germany1. The weighted mean difference for the GMC in girls receiving the 2-dose schedule in Canada 1 is non-inferior to the 3-dose schedule. Results are inconclusive for the other measured outcomes. The published report for Canada1 also provides results at 36 months, when the GMC ratio for HPV16 was non-inferior (0.81. 95% CI 0.55, 1.20) and inconclusive for HPV18 (0.43, 95% CI 0.26, 0.73).

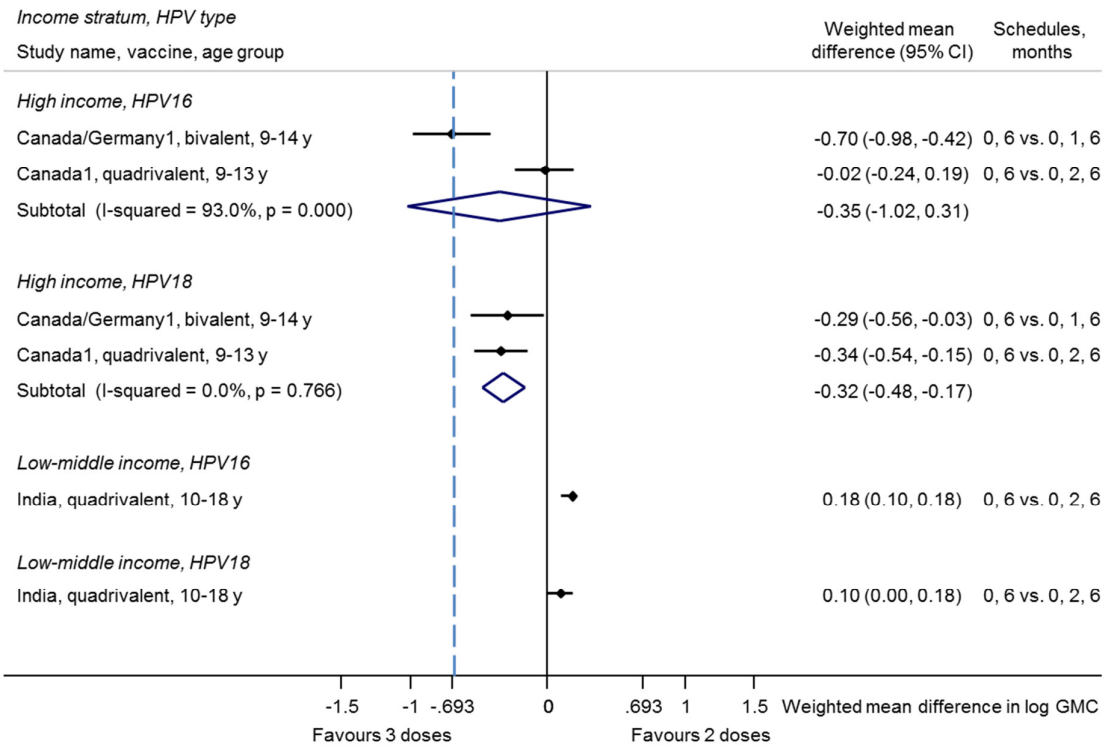

Figure 4. Forest plot, weighted mean difference between GMCs in girls receiving 2-dose and 3-dose schedules, one month after last dose, by income level and HPV type; two trials in high income and one trial in low-middle income strata.

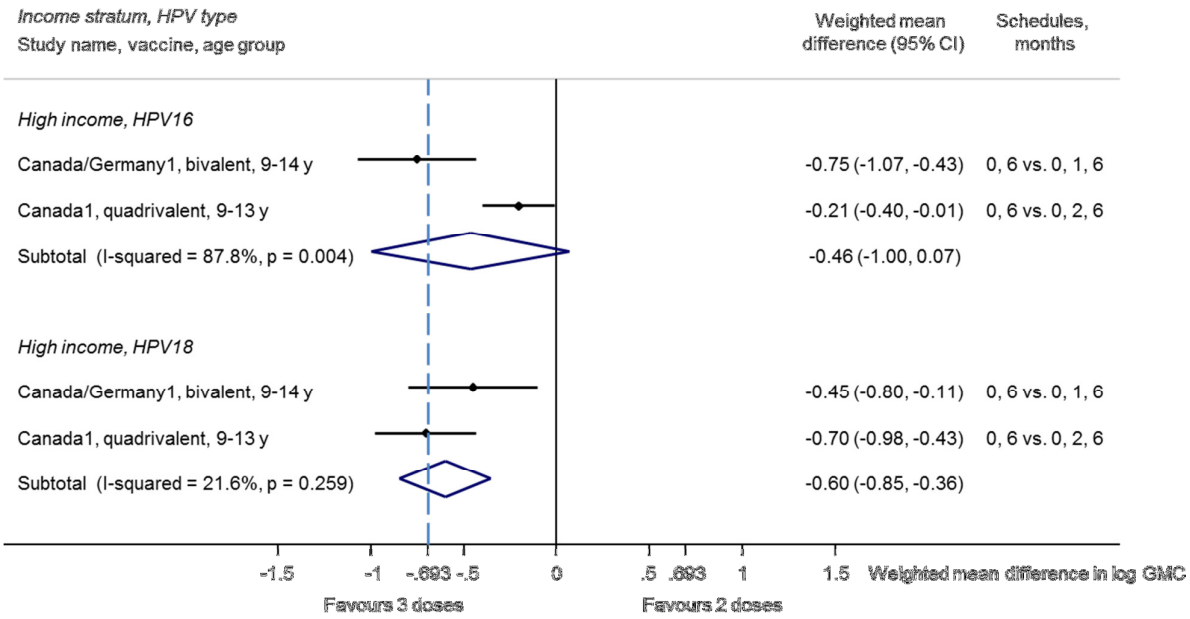

Figure 5. Forest plot, weighted mean difference between GMCs in girls receiving 2-dose and 3-dose schedule, by HPV type, 24 months after last dose; two trials in high income countries.

In both plots, blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

3.2.2 Seroconversion and seropositivity

Canada1 and Canada/Germany1 presented data about seroconversion in girls who were initially seronegative. These results are presented in the text of the articles and describe all participants as being antibody positive for HPV16 and HPV18 one month after the last vaccine dose. In Canada/Germany1 the authors state, "all subjects evaluated at Month 24 were still seropositive" [7]. In Canada1, numerical data are provided in the text [3].

In neither of these trials was there a pre-specified non-inferiority margin for seroconversion. If the non-inferiority margin had been set at 5% (as specified in the Multinational2 trial [8]), the 2-dose schedule in both trials would be non-inferior at all time points for HPV16 in both trials and for HPV18 in Canada/Germany1 (Figure 6). In Canada1, all participants had seroconverted by month 7. At months 24 and 36, fewer participants in the 2-dose than the 3-dose group remained seropositive, but the lower 95% CI includes the non-inferiority margin.

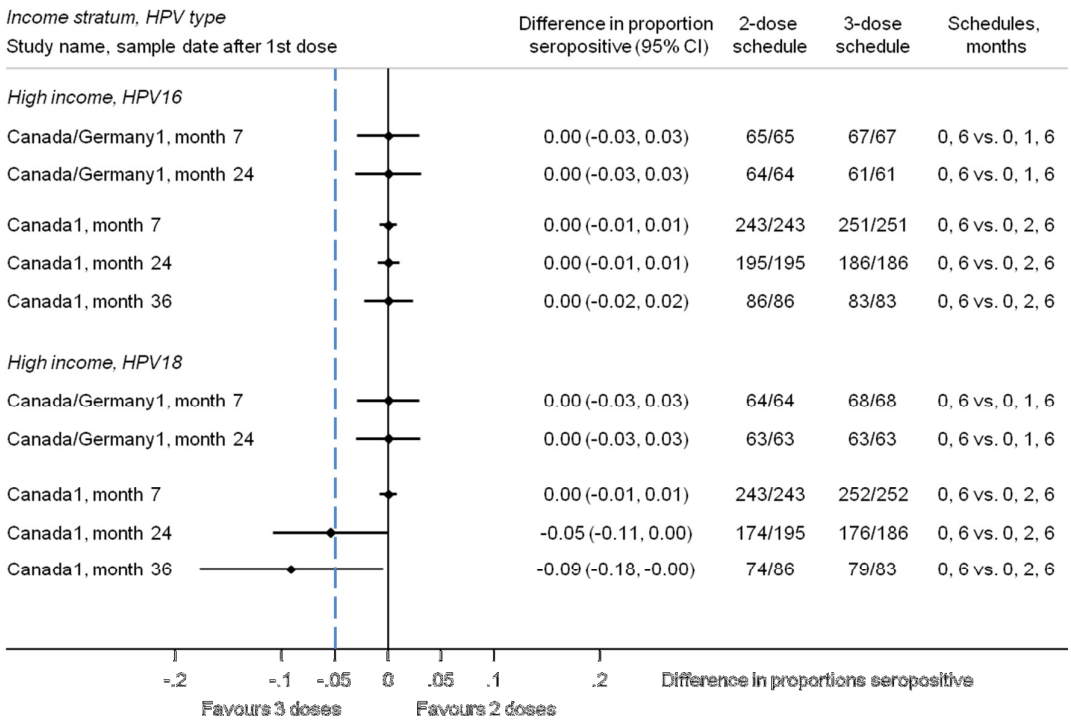

Figure 6. Forest plot of differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose or 3-dose schedule, where data are available.

Horizontal axis is on the natural scale; the solid line at zero represents no difference in % seroconverting between the groups; the blue dashed line at -0.05 is the non-inferiority margin, assumed here to be 5%. The estimates have not been pooled because we present data from all available time points in the same studies.

3.2.3 Clinical outcomes

Limited clinical data were presented at the WHO *ad hoc* meeting in November 2013. The authors reported the frequency of any vaccine type incident infection (HPV6, 11, 16, or 18) in 181 girls aged 18 years or older. Assuming that the results relate to randomised groups, there were more incident infections in the group receiving two doses than three doses.

3.3 Non-randomised comparisons between girls and women

Four studies contributed to this comparison (Canada1, Canada/Germany1, Mexico, Multinational2). Results are stratified into high income and middle income strata. As noted, Multinational2 includes about a fifth of participants from Thailand, which is a middle income country. The numerical data extracted from these RCTs are summarised in Table 7 (appended).

3.3.1 Geometric mean antibody concentrations

All trials met the criteria for non-inferiority trials for both HPV16 and HPV18 (Figure 7). For most comparisons, GMCs were also superior in girls receiving the 2-dose schedule than in women receiving the licensed 3-dose schedule. Only for HPV16 in Canada/Germany1 and Canada1 did the 95% CI include the null effect.

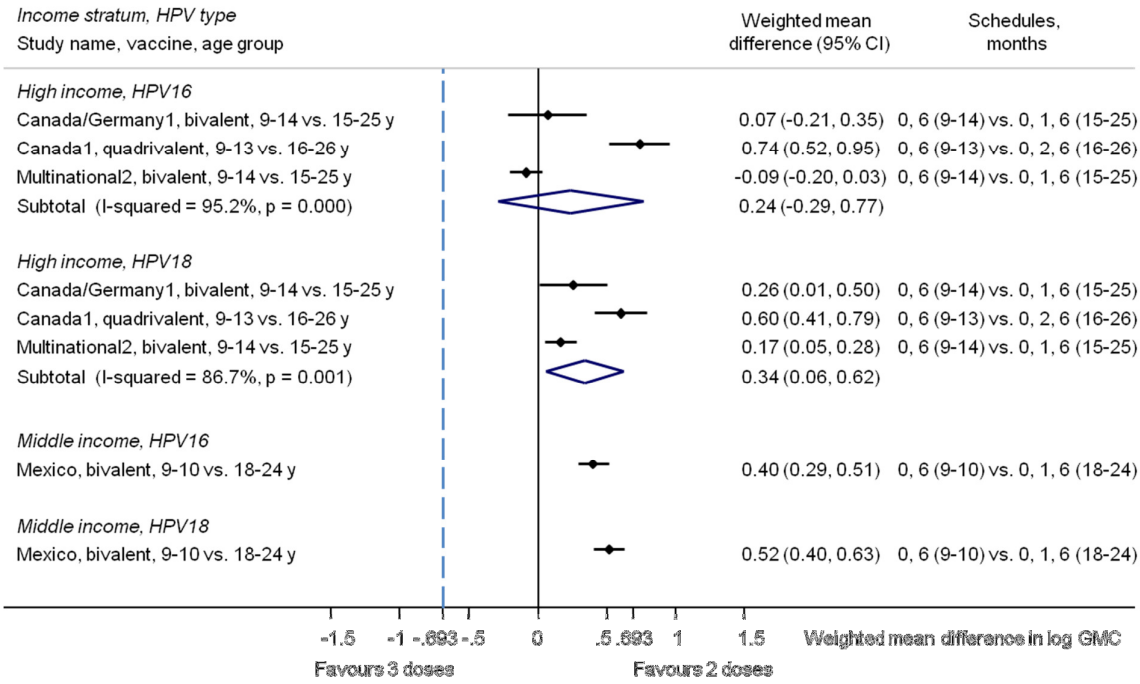

Figure 7. Forest plot, weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule, one month after last dose, by income level and HPV type; three trials in high income and one trial in middle income strata.

Blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

Three trials provided data at later time points; Canada1 at 24 and 36 months, Canada/Germany1 at 24 months and Mexico at 21 months after the first vaccine dose. The data from months 21-24 are shown in Figure 8. The findings and interpretation are similar to those at month seven.

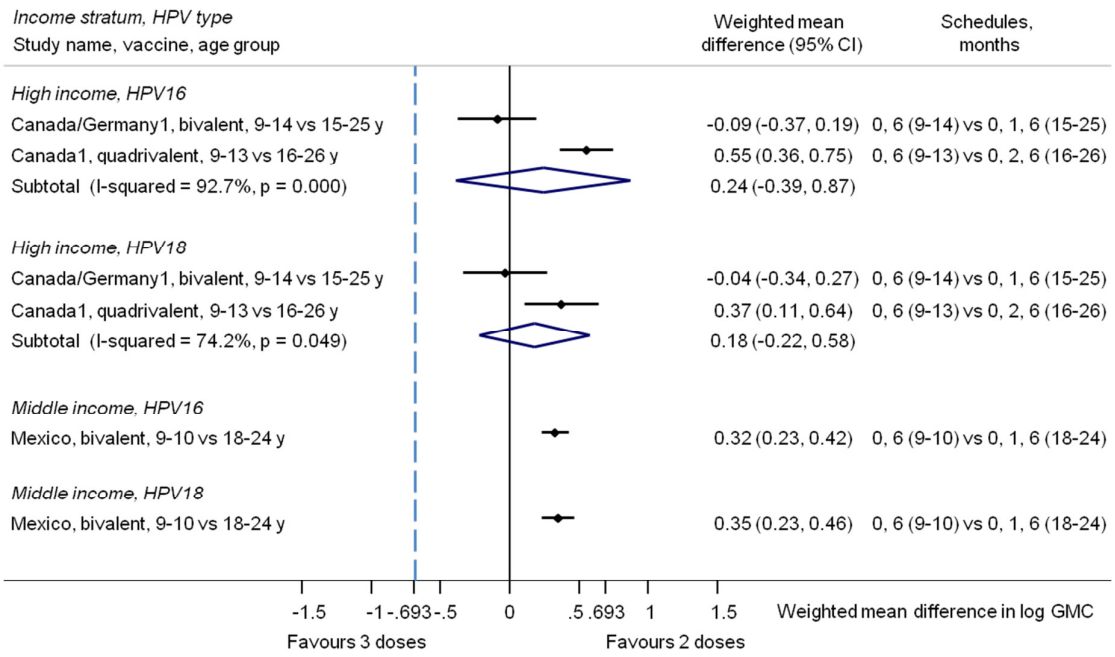

Figure 8. Forest plot, , weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving the licensed 3-dose schedule, 21 months (Mexico) or 24 months (Canada1, Canada/Germany1) after last dose, by income level and HPV type; two trials in high income and one trial in middle income strata.

Blue dashed line shows the non-inferiority margin; $\log_e$ -0.693 is equivalent to a GMC ratio of 0.5 on the natural scale. For non-inferiority of the 2-dose schedule the lower 95% CI of the difference should be less than 0.5 on the natural scale. Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation.

3.3.2 Seroconversion and seropositivity

Data about seroconversion and seropositivity are available for Canada1, Canada/Germany1 and Multinational2 at month seven and for Canada1 (months 24 and 36) and Canada/Germany1 (month 24). The findings are similar to those for girls, with non-inferiority criteria fulfilled. In Canada1, seropositivity in girls at 24 and 36 months was higher than in women who received three doses, although confidence intervals for the differences include the null effect.

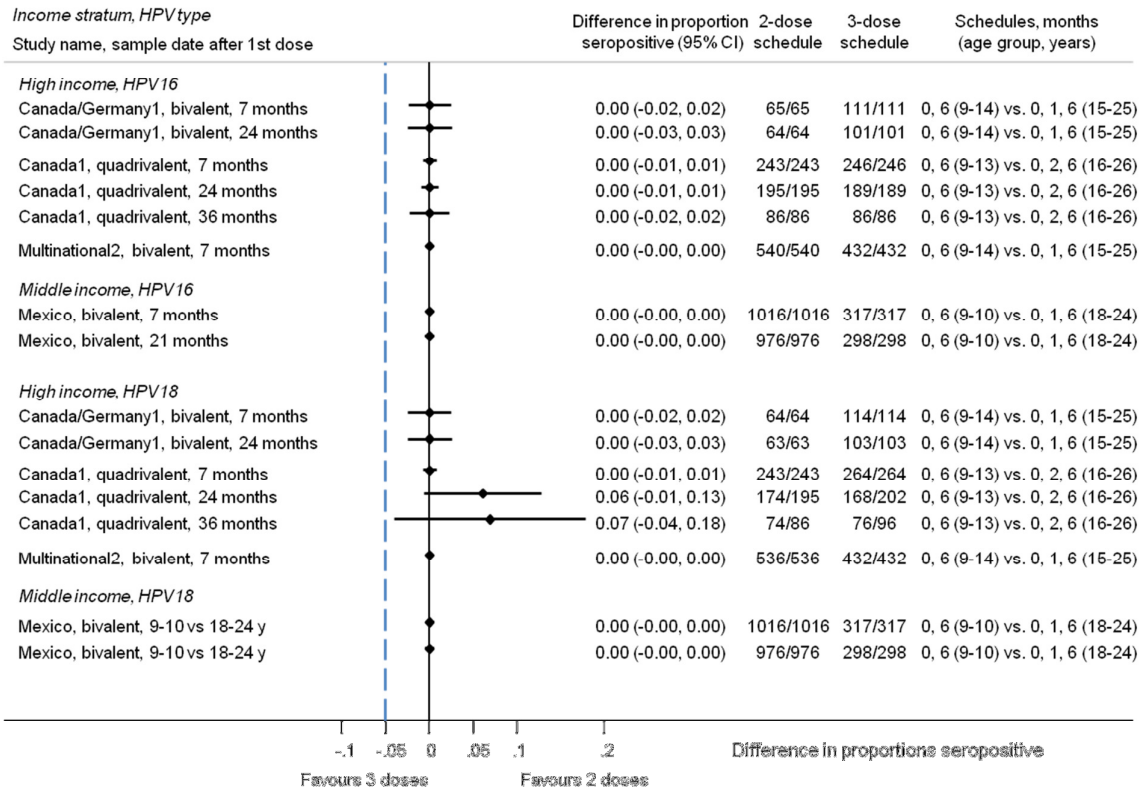

Figure 9. Forest plot of differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose schedule and women receiving the 3-dose schedule, where data are available.

Horizontal axis is on the natural scale; the solid line at zero represents no difference in % seroconverting between the groups; the blue dashed line at -0.05 is the non-inferiority margin, assumed here to be 5%. The estimates have not been pooled because we present data from all available time points in the same studies.

3.3.3 Clinical outcomes

None of the four trials reported on clinical outcomes.

3.3.4 Other comparisons providing evidence

Table 1 summarises five studies that provide additional results about immunological outcomes in randomised comparisons in women (Europe), an observational study of girls (Uganda) and a within-person comparison of girls (Canada3). The overall findings about immunological outcomes support those presented above. Of note, in the Europe trial, the investigators compared women one month after receiving two doses (of an extended 3-dose schedule) at 0, 1 month and women one month after receiving the licensed schedule (0, 1, 6 months). In this comparison of GMCs, the 2-dose schedule was inferior to the 3-dose schedule (weighted mean difference HPV16, -1.17, 95% CI -1.30, -1.05; HPV18, -0.53, 95% CI -0.66, -0.39).

Data about clinical outcomes come from non-randomised comparisons of partially vaccinated women within clinical efficacy trials that enrolled women (CostaRica and Multinationalx). Women receiving two doses at 0 and 1 month were compared to women receiving three doses at 0, 1 and 6 months. These analyses were presented as supporting evidence for the GlaxoSmithKline application to the European Medicines Agency for licensure of the 2-dose schedule [13].

4 Comparison 2: two doses vs. two doses of the same vaccine (different intervals, same dosage and same intervals, different dosage)

We found two RCTs that directly compared two 2-dose schedules (Table 3). One of these (Canada/Germany1) has published results.

Table 3. Summary of comparisons available

Study name, schedule in months (dosage) (age group, years)	GMCs		Seroconversion/ positivity	Clinical
	1 month	Later	Any time point	Any time point
Different interval, same dosage		(24)		
Canada/Germany1, 0, 6 (20µg) vs. 0, 2 (20µg) (9-14 yrs)	+	-	-	-
0, 6 (20µg) vs. 0, 2 (20µg) (15-19 yrs)	+	-	-	-
0, 6 (20µg) vs. 0, 2 (20µg) (20-25 yrs)	+	-	-	-
Multinational2 0, 12 (20µg) vs. 0, 6 (20µg) (9-14yrs)	-	-	-	-
Figure	Figure 10			
Same interval, different dosage				
Canada/Germany1 0, 6 (40µg) vs. 0, 6 (20µg) (9-14yrs)	+	-	-	-
0, 6 (40µg) vs. 0, 6 (20µg) (15-19 yrs)	+	-	-	-
0, 6 (40µg) vs. 0, 6 (20µg) (20-25 yrs)	+	-	-	-
Figure	Figure 11			

Table 4. Summary of studies

Study name [refs], (vaccine)	Alternative study names	Study design details relevant to 2-dose vs. 2-dose comparison	Schedules, months (dosage)	Comparisons presented of 2-dose vs. 2-dose schedules
Primary evidence, controlled trials				
Canada/Germany1 [6-8, 13], (bivalent)	HPV-048	RCT, non-inferiority, dose-range: girls (9-14 yrs); women (15-19, 20-25 yrs) allocated to 2-dose dose schedules	0, 6 (20µg) 0, 2 (20µg) 0, 6 (40µg)	Randomised, different intervals, girls and women Randomised, different dosages, girls and women Immunogenicity
Multinational2 [13, 15, 16] (Canada, German, Italy, Taiwan, Thailand), (bivalent)	HPV-070; GSK 11470; GSK580299	RCT, non-inferiority: girls (9-14 yrs) allocated to two 2-dose schedules;	0, 6 (20µg) 0, 12 (20µg)	Randomised, different intervals, girls No data available yet for this comparison because most recent follow up reported is at 7 months after first vaccine dose
Additional supporting evidence				
Europe [11] (Italy, Romania, Slovakia) (bivalent)	NCT00552279	RCT, non-inferiority: women (15-25 yrs) allocated to two 3-dose schedules. Compared after extended schedule group receives two doses.	0, 1 (12) (20µg)	Single group, women Immunogenicity There is no control/comparison group for these data

4.1 Two dose schedules, comparing different intervals between doses

One trial contributes to this comparison (Canada/Germany1) (there are no data yet available from the Multinational2 study). The investigators compared two 2-dose schedules (0, 2 months and 0, 6 months) with the standard dosage (20µg) of each serotype. The numerical data extracted from these RCTs are summarised in Table 8 (appended).

Data are available for the comparison of GMCs but not seroconversion. The longer interval results in higher GMCs in all age groups. There is no statistical evidence of heterogeneity between the older age groups.

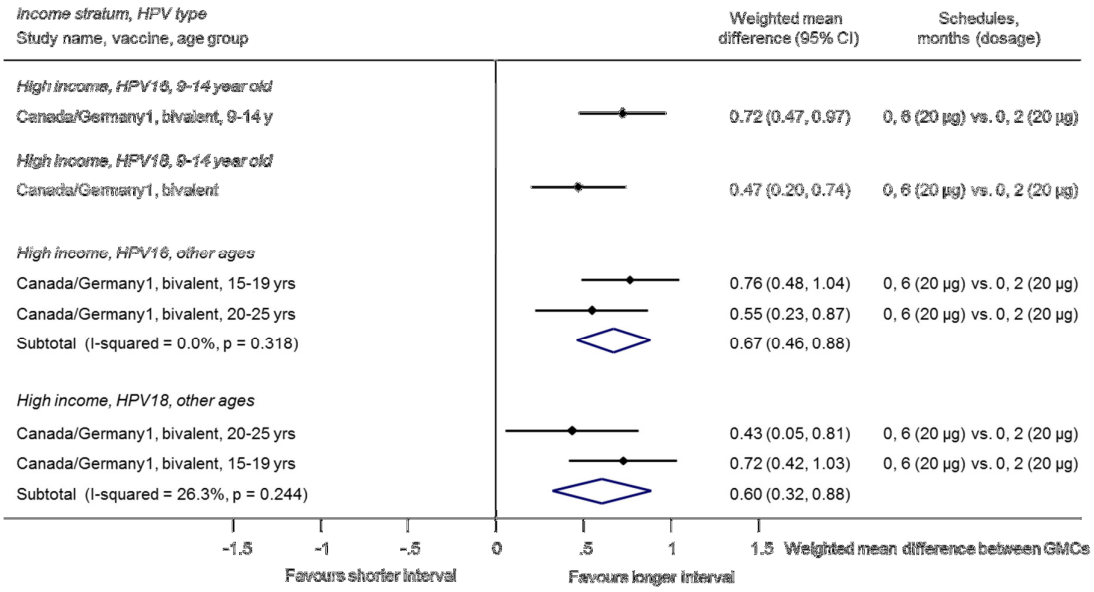

Figure 10. Forest plot, weighted mean difference between GMCs one month after the last vaccine dose in girls (9-14 years) and women at older ages (15-19 and 20-24 years) receiving two doses at 0, 6 months with participants receiving two doses at 0, 2 months.

Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation. Non-inferiority margin not defined because neither schedule is current standard.

4.2 Two dose schedules, comparing different dosages

One trial (Canada/Germany1) provides data about this comparison (Table 3), with randomised comparisons in girls and two older age groups. The numerical data extracted from these RCTs are summarised in Table 9 (appended).

Figure 11 shows that, in all age groups, GMCs are higher in participants who received the higher dosage of vaccine serotypes.

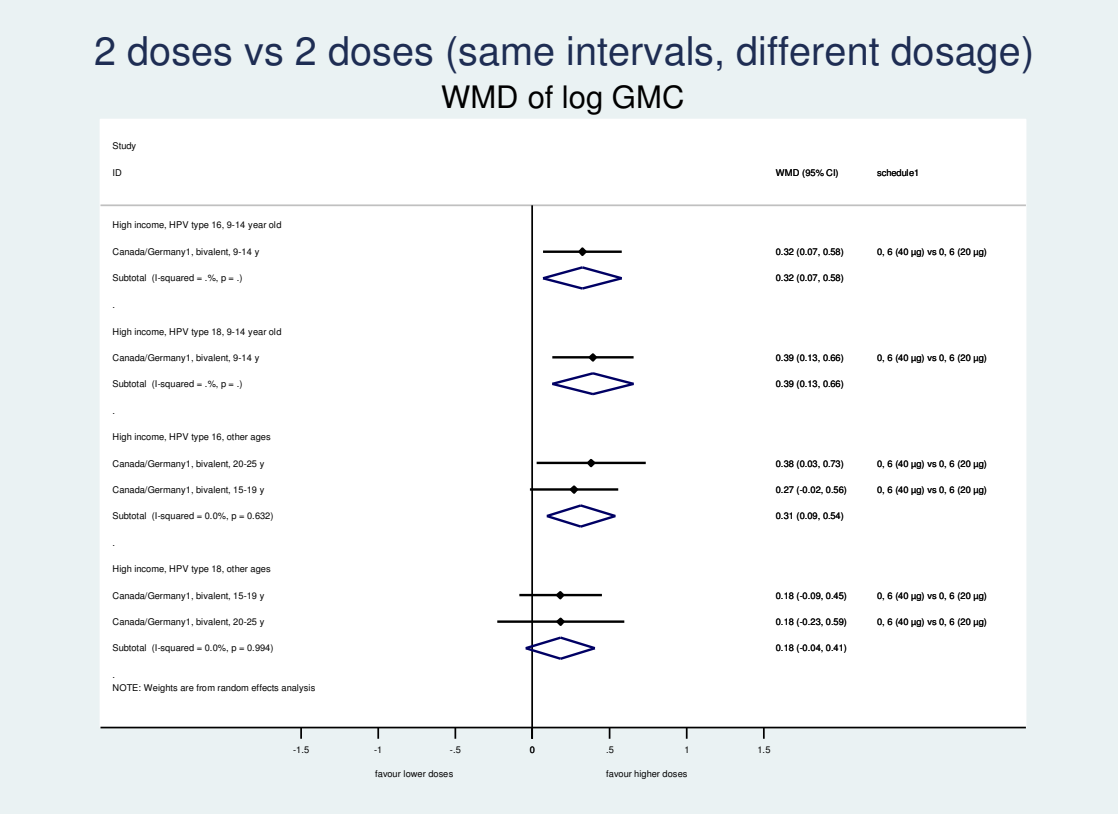

Figure 11. Forest plot, weighted mean difference between GMCs one month after the last vaccine dose in girls (9-14 years) and women at older ages (15-19 and 20-24 years) receiving two doses at 0, 6 months with participants receiving two doses at 0, 2 months.

Blue diamond shows the pooled average difference estimated from random effects meta-analysis. I-squared value is the percentage of heterogeneity between trials due to factors other than random variation. Non-inferiority margin not defined because neither schedule is current standard.

5 Additional tables

Table 5. Summary of RCTs with eligible data for any comparison, grouped together if from the same study.

Table 5. Summary of RCTs with eligible data for any comparison, grouped together if from the same study

Study name, vaccine, ref.	First author, year	Study design	Age group, years	Schedules, months	Outcomes reported	Timing of samples, available data, months (reported timing of samples)*	Comparison available	Comments
Canada1†; quadrivalent [3-5]	Dobson, 2013 Krajden, 2011 Sankaranarayanan, 2013	RCT	9-13	0, 6 0, 2, 6	GMC (mMU/mL) Seropositivity	0, 7, 18, 24, 36	2 vs 3 doses	
			9-13 16-26	0, 6 0, 2, 6	GMC (mMU/mL) Seropositivity	0, 7, 18, 24, 36	2 vs 3 doses, not randomised	Schedule assigned according to age no randomisation (2 doses for girls, 3 doses for women)
Canada, Germany1; bivalent [6-8, 13]	Romanowski, 2011 Romanowski, 2013 GSK, n110659, 2010 (HPV 048)	RCT	9-14	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7, 24 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			15-19	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			20-25	0, 6 (20µg) 0, 1, 6 (20µg) 0, 6 (40 µg) 0, 2 (40 µg)	GMC (EU/mL) seropositivity‡	0, 7 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses 2 vs 2 (different interval, same dose) 2 vs 2 (same interval, different dose)	
			9-14 15-25	0, 6 (20µg) 0, 1, 6 (20µg)	GMC (EU/mL) seropositivity‡	0, 7, 24 (0, 3§, 7, 12, 18, 24)	2 vs 3 doses, not randomised	Schedule assigned according to age no randomisation (2 doses for girls, 3 doses for women)
Canada2; quadrivalent [17-19]	Sauvageau, Gilca, 2013 Sauvageau, 2012 NCT02009800	RCT	9-10	0, 6 0, 6, 60	NR	NR	2 vs 3 doses	Results not available Study start date November 2013
Canada3;	Gilca, 2013	RCT	9-10	0, 6	NR	NR	2 vs 3 doses	Results not described in

quadrivalent [12, 18, 28-30]	Sauvageau, 2013 Sauvageau, Gilca, 2013			0, 6, 42				this report because comparison 2 vs. 3 was made in the same individuals
Europe; bivalent [11]	Esposito, 2011	RCT	15-25	0, 1, 6 0, 1, 12	GMC, Seroconversion rate, safety	0, 2, 7, 13	3 vs 3 doses	
			15-25	0, 1, 0, 1, 6	GMC, Seroconversion rate, safety	0, 2, 7	2 vs 3 doses	
			15-25	0, 1 0, 1, 12	GMC, Seroconversion rate, safety	0, 2, 13	2 vs 3 doses	
Europe1; quadrivalent (vs 9-valent) (ID 71)	Van Damme P, 2013	RCT	9-15	All given at 0, 2, 6 HPV16: 40 vs. 60µg/dose HPV18: 20 vs. 40µg/dose	GMC, Seroconversion rate	0, 7	3 vs 3 doses (different dosage, same interval)	
India; quadrivalent [5, 9] ‖	Sankaranarayanan R, 2013 Sankaranarayanan R, 2013	RCT	10-18	0, 6 0, 2, 6	FMI, GMC (mMU/mL), Seropositivity, Frequency of incident and persistent HPV 16/18/6/11 infection	0, 7, 18 (0, 7, 12, 18, 24, 36, 48)	2 vs 3 doses	Methods described based on meeting presentation and conference abstracts only.
Multinational2, bivalent [13, 15, 16]	GSK, n 114700, 2013 (HPV 070) Phutanakit, 2013	RCT	9-14	0, 6 0, 12	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 2 dose, No data available	No GMC data available at month 13, only data at month 7 after first dose
			9-14 15-25	0, 6 0, 1, 6	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 3 doses, not randomized	Schedule assigned according to age no randomization (2 doses for girls, 3 doses for women) Schedule assigned

			9-14 15-25	0, 12 0, 1, 6	GMC (EU/mL), Seropositivity, Seroconversion, CMI	0, 7 (0, 7, 12, 18, 24, 36)	2 vs 3 doses, not randomized; No data available	according to age no randomization (2 doses for girls, 3 doses for women). No data at month 13
Multinational4, [25, 26] (bivalent and quadrivalent)	NCT01462357 EUCTR2011-002035-26-SE	RCT	9-14	0, 6 bivalent 0, 6 0, 2, 6 quadrivalent	GMC, seroconversion	(0, 7, 12, 18, 24, 36)	2 vs 3 doses No data avaliable	Results not available
Peru; quadrivalent[32, 33]	Brown, 2012 NCT00925288	RCT	18-26	0, 2, 6 0, 3, 6	GMC	0, 7	3 vs 3 doses (different interval, same dosage)	
USA 2; quadrivalent [34]	Zimmermann, 2010	RCT	18-23	0, 2, 6 0, 2, 12	GMC, seropositivity¶	0, 7 0, 13	3 vs 3 doses (different interval, same dosage)	
USA; quadrivalent	Lin, 2014(ID1005)	RCT	18-25 (male)	0, 2, 6 0, 2, 12	GMC	0, 7 0, 13	3 vs 3 dose (different interval, same dosage)	
USA; quadrivalent	Villa, 2006 (ID1343)	RCT	16-23	0, 2, 6 (20 µg) 0, 2, 6 (40 µg) 0, 2, 6 (80 µg)	GMC	(0, 2, 7, 36)	3 vs 3 doses (same interval, different dosage), No data available	Data not available
Vietnam; quadrivalent [35, 36]	Neuzil, 2011 LaMontagne, 2013	RCT	11-13	0, 2, 6	GMC	6, 7, 35 (0, 6, 7, 35)	3 vs 3 doses (different interval, same dosage)	
				0, 3, 9		9, 10, 41 (0, 9, 10, 41)	3 vs 3 doses (different interval, same dosage)	
				0, 6, 12		12, 13, 44 (0, 12, 13, 44)	3 vs 3 doses (different interval, same dosage)	
				0, 12, 24		24, 25, 56 (0, 24, 25, 44, 56)	3 vs 3 doses (different interval, same dosage)	

Abbreviations: RCT, randomised controlled trial; GMC, Geometric mean concentration; GMCs, Geometric mean concentration ratio; MFI, mean fluorescence index (serum antibodies seems to be tested using a competitive Luminex immunoassay (cLIA)); CMI, specific T-cell and B-cell mediated immune responses; NR, not reported; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† Designed as noninferiority immunogenicity study

‡ Seropositivity defined as ≥8 ELISA units [EU]/mL for HPV 16 antibodies and ≥7 EU/mL for HPV 18

§ Only for the 0, 2 months group

‖ Assumes that study reported in Eurogin abstract SS17-7 is the same trial as NCT00923702, and that text refers to results 1 month after the last dose;

¶ Seropositivity defined as anti-HPV serum cLIA (competitive Luminex immunoassay) levels ≥20 milliMerck (mM) units/mL for HPV types 6 and 16, ≥16mM units/mL for type 11, and ≥24mM units/mL for type 18

Table 6. Randomised comparisons between 2-dose and 3-dose schedules, by study and types of outcome

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Results 2 doses	Results 3 doses	Ratio 2:3 dose	Additional data
Geometric mean concentrations						**2 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**3 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**2:3 dose GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†**	**2:3 dose GMC ratio (95% CI), latest time point available, per protocol†**
Canada 1; quadrivalent [3-5]	9-13	0, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16	7457 (6388-8704)	7640 (6561-8896)	0.98 (0.75-1.27)	0.81 (0.55-1.20) ‡
		0, 2, 6			HPV 18	1207 (1054-1384)	1703 (1489-1946)	0.71 (0.56-0.89)	0.43 (0.26-0.73) ‡
Canada/Germany 1; bivalent [6-8]	9-14	0, 6	EU/mL	0, 7, 24	HPV 16	11067 (9190-13328)	22261 (18034-27480)	0.50 (0.38-0.66)	0.47 (0.34-0.65) §
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	5510 (4646-6535)	7399 (6033-9073)	0.74 (0.57-0.97)	0.64 (0.45-0.90) §
	15-19	0, 6	EU/mL	0, 7	HPV 16	8442 (6895-10336)	12858 (9696-17051)	0.66 (0.46-0.93)	NR
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	5142 (4354-6072)	4845 (3740-6277)	1.06 (0.78-1.45)	NR
	20-25	0, 6	EU/mL	0, 7	HPV 16	5673 (4377-7354)	7971 (5766-11020)	0.71 (0.47-1.07)	NR
		0, 1, 6		(0, 7, 12, 18, 24)	HPV 18	3523 (2514-4937)	3676 (2898-4664)	0.96 (0.63-1.45)	NR

Europe; bivalent [11]	15-25	0, 1 0, 1, 12	EU/mL	0, 2, 13	HPV 16 HPV 18	3117 (2874.8-3379.7) 2271 (2080.6-2478.8)	11884 (10676.6-13229.6) 4501.3 (4067.7-4981.1)	0.31 (0.27-0.35) 0.59 (0.52-0.68)	NR NR
	15-25	0, 1 0, 1, 6	EU/mL	0, 2, 7	HPV 16 HPV 18	3194.7 (2939-3472.6) 2338.3 (2129.2-2567.9)	10311.9 (9390.2-11324.2) 3963.6 (3589.4-4376.8)	0.26 (0.23-0.30) 0.51 (0.44-0.58)	NR NR
						Mean MFI	Mean MFI	MFI ratio (95% CI)	MFI ratio (95% CI)
India; quadrivalent [5, 9]	10-18	0, 6 0, 2, 6	mMU/ mL	0, 7, 18 (0, 7, 12, 18, 24, 36, 48)	HPV 16 HPV 18	6706.1 3851.7	5806.8 3445.7	1.2 (1.1-1.2) 1.1 (1.0-1-2)	0.6 (0.5-0.7) ‖ 0.5 (0.4-0.6) ‖
Seronconversion/seropositivity						**2 doses, Seroconversion/ seropositivity**	**3 doses, Seroconversion/ seropositivity**		
						7m after dose 1	7m after dose 1		
Canada 1; quadrivalent [3-5]	9-13	0, 6 0, 2, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16 HPV 18	243/243 (100%) 243/243 (100%)	251/251 (100%) 252/252 (100%)		
						24 months after dose 1	24 months after 1st dose		
					HPV 16 HPV 18	195/195 (100%) 174/195 (89%)	186/186 (100%) 176/187 (94%)		
						36 months after dose 1	36 months after dose 1		
					HPV 16 HPV 18	86/86 (100%) 74/86 (86%)	83/83 (100%) 79/83 (95%)		
						7m after dose 1	7m after dose 1		
Canada/Germany	9-13	0, 6	mMU/	0, 7, 18, 24, 36	HPV 16	65/65 (100%)	67/67 (100%)		

1; bivalent [6-8]		0, 2, 6	mL		HPV 18	64/64 (100%)	68/68 (100%)		
						24 months after dose 1	24 months after dose 1		
					HPV 16	64/64 (100%)	61/61 (100%)		
					HPV 18	63/63 (100%)	64/64 (100%)		
						1 month after last dose	1 month after last dose		
Europe; bivalent [11]	15-25	0, 1	EU/mL	0, 2	HPV 16	(100%) ¶	337/337 (100%)		
		0, 1, 12		0, 2, 13	HPV 18	(100%) ¶	346/345 (99.7%)		
	15-25	0, 1	EU/mL	0, 2	HPV 16	(100%) ¶	342/342 (100%)		
		0, 1, 6		0, 2, 7	HPV 18	(100%) ¶	346/346 (100%)		
Clinical						**2 doses, clinical outcome**	**3 doses, clinical outcome**	**Clinical outcome**	**Clinical outcome**
India; quadrivalent [5, 9]	10-18	0, 6	mMU/ mL	0, 7, 12, 24, 36, 48	All HPV type	Frequency of HPV incident infection	Frequency of HPV incident infection		
		0, 2, 6				6/36 (17%)	1/44 (2%)		

Abbreviations: GMC, Geometric mean concentration; GMCs, Geometric mean concentration ratio; FMI, mean fluorescence index (serum antibodies seems to be tested using a competitive Luminex immunoassay (cLIA)); NR, not reported; EU/ml, ELISA units per millilitre; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs

‡ latest time point available, month 36

§ latest time point available, month 24

‖ latest time point available, month 18

¶ Number of individuals with blood sample at this time point not reported, in forest plots we have used the denominator for month 7 per protocol data (for group 0, 1 vs 0, 1, 12 we used HPV16= 342 and HPV18=346; for group 0, 1 vs 0, 1, 6 we used HPV16= 337 and HPV18=346)

Table 7. Available results for geometric mean concentrations and seropositivity in non-randomised comparisons of two doses in girls vs. three doses in women

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Results 2 doses	Results 3 doses	Ratio 2:3 dose	Additional ratio 2:3 dose
Immunogenicity, GMC						**2 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**3 doses, GMC (95% CI), 1 month after last vaccine dose, per protocol**	**2:3 dose GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†**	**2:3 dose GMC ratio (95% CI), latest time point available, per protocol†**
Canada1; quadrivalent [3-5]	9-13	0, 6	mMU/mL	0, 7, 18, 24, 36	HPV 16	7457 (6388-8704)	3574 (3065-4169)	2.10 (1.68-2.59)	1.70 (1.16-2.49) ‡
	16-26	0, 2, 6			HPV 18	1207 (1054-1384)	661 (580-754)	1.82 (1.51-2.20)	1.46 (0.88-2.41) ‡
Canada/Germany1; bivalent [6-8]	9-14	0, 6 (20 µg)	EU/mL	0, 7, 24	HPV 16	11067 (9190-13328)	10322 (8329-12792)	1.07 (0.81-1.42)	0.91 (0.69-1.21) §
	15-25	0, 1, 6 (20 µg)		(0, 7, 12, 18, 24)	HPV 18	5510 (4646-6535)	4262 (3572-5084)	1.30 (1.01-1.65)	0.96 (0.71-1.31) §
Mexico, Lazcano-Ponce 2013 [23] ‖	9-10	0, 6	EU/mL	0, 7, 21	HPV 16	10442 (9894-11020)	6991 (6333-7717)	1.49 (1.34-1.67)	1.37 (1.26-1.52) ¶
	18-24	0, 1, 6		(7, 21, 60, 72, 120)	HPV 18	5837 (5517-6175)	3483 (3164-3834)	1.68 (1.49-1.88)	1.37 (1.26-1.58) ¶
Multinational2, GSK, n 114700, 2013 Phutanakit, 2013[15, 16]	9-14	0, 6	EU/mL	0, 7	HPV 16	9400 (8818.3-10020.4)	10234 (9258.3-11313.6)	0.91 (0.82-1.03)	NR
	15-25	0, 1, 6		(0, 7, 12, 18, 24, 36)	HPV 18	5909.1 (5508-6338)	5002.6 (4572-5473.1)	1.18 (1.05-1.32)	NR

Uganda, Safaeian 2012, [34] **	12-20	< 3 doses vs 3 doses	NR	NR	HPV 16	NR	NR	NR	0.51 (0.37-0.69)
					HPV 18	NR	NR	NR	0.69 (0.5-0.96)

Seropositivity						**2 doses, Seropositivity/ Seroconversion**	**3 doses, Seropositivity/ Seroconversion**	**2 doses – 3 doses, difference in proportions (95% CI)**
						7 months after 1 dose	7 months after 1 dose	
Canada1; quadrivalent [3-5]	9-13	0, 6	mMU/ mL	0, 7, 18, 24, 36	HPV 16	243/243 (100%)	246/246 (100%)	To follow
	16-26	0, 2, 6			HPV 18	243/243 (100%)	264/264 (100%)	
						24 months after 1 dose	24 months after 1 dose	
					HPV 16	195/195 (100%)	189/189 (100%)	To follow
					HPV 18	174/195 (89%)	168/202 (83%)	
						36 months after 1 dose	36 months after 1 dose	
					HPV 16	86/86 (100%)	86/86 (100%)	To follow
					HPV 18	74/86 (86%)	76/96 (79%)	
						1 month after last dose	1 month after last dose	
Canada/Germany1 ; bivalent [6-8]	9-14	0, 6 (20 µg)	EU/mL	0, 7, 12, 24	HPV 16	65/65 (100%)	111/111 (100%)	To follow
	15-25	0, 1, 6 (20 µg)		(0, 7, 12, 18, 24)	HPV 18	64/64 (100%)	114/114 (100%)	
						24 months after 1 dose	24 months after 1 dose	
					HPV 16	64/64 (100%)	101/101 (100%)	To follow
					HPV 18			

						63/63 (100%)	103/103 (100%)
						7 months after 1 dose	7 months after 1 dose
Mexico, Lazcano-Ponce 2013 [14]	9-10	0, 6	EU/mL	0, 7, 21	HPV 16	1016/1016 (100%)	317/317 (100%)
	18-24	0, 1, 6			HPV 18	1016/1016 (100%)	317/317 (100%)
						21 months after 1 dose	21 months after 1 dose
					HPV 16	976/976 (100%)	298/298 (100%)
					HPV 18	976/976 (100%)	317/317 (100%)
						1 month after last dose	1 month after last dose
Multinational2, GSK, n 114700, 2013 Phutanakit, 2013[15, 16]	9-14	0, 6	EU/mL	0, 7	HPV 16	540/540 (100%)	432/432 (100%)
	15-25	0, 1, 6		(0, 7, 12, 18, 24, 36)	HPV 18	536/536 (100%)	432/432 (100%)

Abbreviations: GMC, Geometric mean concentration; NR, not reported; EU/ml, ELISA units per millilitre; mMU/ml, milli-Merck units per millilitre;

* Reported as time since first dose; months outside brackets are available data

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs

‡ latest time point available, month 36

§ latest time point available, month 24

‖ This study is not a RCT; the data are included here because there is a comparison between 2 doses in girls and 3 doses in women. See table 8.

¶ latest time point available, month 21

** No numerical results for this study. Abstract only available. See table 2.

Table 8. Comparisons between 2-dose vs. 2-dose schedules (different interval, same dosage)

Study name; vaccine [refs]	Age, years	Schedule compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Schedule 1, GMC (95% CI), 1 month after last vaccine dose, per protocol	Schedule 2 (95% CI), 1 month after last vaccine dose, per protocol	Schedule 1:2 GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†	Schedule 1:2 GMC ratio (95% CI), latest time point available, per protocol†
						Longer interval	*Shorter interval*	*Longer:shorter*	*Longer:shorter*
Canada/Germany 1; bivalent [6-8]	9-14	0, 6 (40 µg)	EU/mL	0, 7, 24 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	15304 (12855-18221)	7,442 (6238-8878)	2.05 (1.60-2.64)	1.93 (1.43-2.64) §
		0, 2 (40 µg)			HPV 18	8155 (6671-9970)	5095 (4288-6140)	1.60 (1.22-2.10)	2.18 (1.54-3.10) §
	15-19	0, 6 (40 µg)	EU/mL	0, 7 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	11061 (9035-13541)	5153 (4246-6254)	2.14 (1.62-2.83)	NR
		0, 2 (40 µg)			HPV 18	6162 (4996-7601)	2986 (2385-3740)	2.05 (1.52-2.80)	NR
	20-25	0, 6 (40 µg)	EU/mL	0, 7 (0, 3,‡ 7, 12, 18, 24, 48)	HPV 16	8307 (6533-10564)	4809 (3886-5952)	1.73 (1.26-2.39)	NR
		0, 2 (40 µg)			HPV 18	4230 (3346-5349)	2742 (2031-3701)	1.54 (1.05-2.25)	NR

Abbreviations: GMC, Geometric mean concentration; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre; NR, not reported; RCT, randomised controlled trial;

* All reported time points, in months since first dose; months outside brackets are available data;

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs;

‡ Only for the 0, 2 months group

§ latest time point available, month 24

Table 9. Comparisons between 2-dose vs. 2-dose schedules (different dosage, same interval)

Study name; vaccine [refs]	Age, years	Dosage compared, months (dose 20µg unless stated)	GMC units	Timing of samples, available data in months (timing of samples, according to methods)*	HPV type	Dosage 1, GMC (95% CI), 1 month after last vaccine dose, per protocol	Dosage 2 (95% CI), 1 month after last vaccine dose, per protocol	Dosage 1:2 GMC ratio (95% CI), 1 month after last vaccine dose, per protocol†	Dosage 1:2 GMC ratio (95% CI), latest time point available, per protocol†
						Higher dose	*Standard dose*	*Higher:standard*	*Higher:standard*
Canada/Germany 1; bivalent [6-8]	9-14	0, 6 (40 µg)	EU/mL	0, 7, 24 (0, 7, 12, 18, 24, 48)	HPV 16	15304 (12855-18221)	11067 (9190-13328)	1.38 (1.07-1.79)	NR (1.4) ‡
		0, 6 (20 µg)			HPV 18	8155 (6671-9970)	5510 (4646-6535)	1. 48 (1.14-1.94)	NR (1.4) ‡
	15-19	0, 6 (40 µg)	EU/mL	0, 7 (0, 7, 12, 18, 24, 48)	HPV 16	11061 (9035-13541)	8442 (6895-10336)	1.31 (0.98-1.75)	NR
		0, 6 (20 µg)			HPV 18	6162 (4996-7601)	5142 (4354-6072)	1.20 (0.92-1.57)	NR
	20-25	0, 6 (40 µg)	EU/mL	0, 7 (0, 7, 12, 18, 24, 48)	HPV 16	8307 (6533-10564)	5673 (4377-7354)	1.46 (1.03-2.08)	NR
		0, 6 (20 µg)			HPV 18	4230 (3346-5349)	3523 (2514-4937)	1.20 (0.79-1.80)	NR

Abbreviations: GMC, Geometric mean concentration; EU/ml, ELISA units per millilitre; LU, Luminex units; mMU/ml, milli-Merck units per millilitre; NR, not reported; RCT, randomised controlled trial;

* All reported time points, in months since first dose; months outside brackets are available data;

† If GMC ratio not reported in text, point estimate has been calculated from reported GMCs;

‡ latest time point available, month 24

6 References

1. Einstein, M.H., *Module 19: Human papillomavirus infection*, in *The Immunological Basis for Immunization Series*. 2010, World Health Organization: Geneva.
2. Velicer, C., et al., *Prevalence and incidence of HPV genital infection in women.* Sex Transm Dis., 2009. **36**(11): p. 696-703. doi: 10.1097/OLQ.0b013e3181ad25ff.
3. Dobson, S.R., et al., *Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial.* JAMA, 2013. **309**(17): p. 1793-1802.
4. Krajden, M., et al., *Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two- versus three-dose HPV vaccine trial.* Clin Vaccine Immunol, 2011. **18**(3): p. 418-23.
5. Sankaranarayanan, R., *2 vs 3 doses hpv vaccine schedule: low- and middle-income countries*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.
6. Romanowski, B., et al., *Immune response to the hpv-16/18 as04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.
7. Romanowski, B., et al., *Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study.* Hum Vaccin, 2011. **7**(12): p. 1374-86.
8. GlaxoSmithKline. *Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 – 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing.* 2013 [cited 2013 Nov 14]; Available from: http://download.gsk-clinicalstudyregister.com/files/ebe3f40a-ef27-469c-8874-35053b5a80d7.
9. Sankaranarayanan, R. *Trial of Two Versus Three Doses of Human Papillomavirus (HPV) Vaccine in India*. 2013 [cited 2013 Nov 15]; Available from: http://clinicaltrials.gov/show/NCT00923702.
10. Sankaranarayanan, R., *Evaluation of Fewer Than Three Doses of HPV Vaccination in India*, in *WHO Consultation Meeting*. 2013: WHO, Geneva.
11. Esposito, S., et al., *Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted vaccine administered according to an alternative dosing schedule compared with the standard dosing schedule in healthy women aged 15 to 25 years: results from a randomized study.* Pediatr Infect Dis J, 2011. **30**(3): p. e49-55.
12. Québec, I.N.d.S.P.d., *HPV Vaccination in Québec: Knowledge Update and Expert Panel Proposals*. Institut National de Santé Publique du Québec: Québec, Canada. p. 37-59.
13. EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Assessment report EMA/789820/2013 Cervarix* 2013 21st November 2013.
14. Lazcano-Ponce, E.S., M.; Muñoz, N.; Torres, L.; Cruz-Valdez, A.; Salmerón, J.; Rojas, R.; Herrero, R.; Hernández-Ávila, M, *Overcoming barriers to HPV vaccination: Non-inferiority of Antibody Response to Human Papillomavirus 16/18 Vaccine in Adolescents Vaccinated with a Two-dose vs. a Three-dose Schedule at 21 Months.* 2013.
15. GlaxoSmithKline. *Immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 L1 AS04 vaccine when administered according to alternative 2-dose schedules in 9 - 14 year old females.* 2013 [cited 2013 Nov 14]; Available

from: http://download.gsk-clinicalstudyregister.com/files/1ae03c85-a5fe-4339-a1e1-03a3d97f6793.

16. Puthanakit, T., et al., *Immune responses to a 2-dose schedule of the hpv-16/18 as04-adjuvanted vaccine in girls (9-14) versus 3 doses in women (15-25): a randomised trial*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.

17. Sauvageau, C., et al., *Protocole ICI-VPH: Impact des calendriers d'immunisation contre les VPH*. 2013, Québec: ministères de la Santé et des Services sociaux.: Québec, Canada. p. 28p.

18. Institut National de Santé Publique du Québec. *La vaccination des pré-adolescents contre les virus du papillome humain (VPH) au Québec : deux ou trois doses?* 2013 [cited 2013 Nov 14]; Available from: http://www.inspq.qc.ca/pdf/publications/1683_VaccinPreAdoVPHQc_2ou3Doses.pdf.

19. NCT02009800. *ICI-VPH: Impact of HPV Immunisation Schedules Against HPV*. March 15, 2013 [cited 2014 10.01.2014]; Available from: http://ClinicalTrials.gov/show/NCT02009800.

20. Kreimer, A.R., *Overview of the Costa Rica HPV vaccine trial*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.

21. Kreimer, A.R., et al., *Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial.* Lancet Oncol., 2011. **12**(9): p. 862-70. doi: 10.1016/S1470-2045(11)70213-3. Epub 2011 Aug 22.

22. Kreimer, A.R., et al., *Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine.* J Natl Cancer Inst, 2011. **103**(19): p. 1444-51.

23. Safaeien, M., *Immunogenicity and efficacy of hpv vaccines based on fewer doses*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.

24. Arguedas, A., et al., *Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines.* Vaccine., 2010. **28**(18): p. 3171-9. doi: 10.1016/j.vaccine.2010.02.045. Epub 2010 Feb 26.

25. EUCTR2011-002035-26-SE. *Immunogenicity and safety study of GlaxoSmithKline Biologicals' HPV vaccine (GSK-580299) and Merck's Gardasil® vaccine when administered according to alternative 2-dose schedules in 9-14 years old females GSK 115411*. [cited 2014 24.01.2014]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-002035-26.

26. NCT01462357. *Immunogenicity and Safety Study of GlaxoSmithKline Biologicals' Human Papillomavirus (HPV) Vaccine (GSK-580299) and Merck's GardasilÂ® Vaccine When Administered According to Alternative 2-dose Schedules in 9-14 Year Old Females*. September 6, 2013 [cited 2014 10.01.2014]; Available from: http://ClinicalTrials.gov/show/NCT01462357.

27. Safaeien, M., *Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda*, in *28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326*. 2012: San Juan, Puerto Rico. p. 326.

28. Gilca, V. and C. Sauvageau, *Immunogenicity of one and two doses of Gardasil in 9-10 year-old girls and the effect of a booster dose of Gardasil or Cervarix given 3 years later*, in *WHO Consultation Meeting*. 2013: WHO, Geneva.

29. Sauvageau, C., et al., *Two doses of quadrivalent hpv vaccine might be sufficient when vaccinating preadolescents*, in *Eurogin 2013 International Multidisciplinary Congress*. 2013: Florence, Italy.

30. Gilca, V., *Interchangeable use of Gardasil and Cervarix: preliminary safety data*, in *28th International Papillomavirus Conference*. 2012: San Juan, Puerto Rico.

31. Ogilvie, G., et al., *QUEST: Quadrivalent HPV Vaccine Evaluation Study.* , Vancouver: BC Centre for Disease Control, 27p, Editor. 2012.

32. NCT00925288. *Acceptability of Human Papillomavirus (HPV) Vaccine in Female Sex Workers*. February 2, 2012 [cited 2014 10.01.2014]; Available from: http://ClinicalTrials.gov/show/NCT00925288.

33. Brown, B., et al., *Randomized trial of HPV4 vaccine assessing the response to HPV4 vaccine in two schedules among Peruvian female sex workers.* Vaccine., 2012. **30**(13): p. 2309-14. doi: 10.1016/j.vaccine.2012.01.058. Epub 2012 Feb 1.

34. Zimmerman, R.K., et al., *Randomized trial of an alternate human papillomavirus vaccine administration schedule in college-aged women.* J Womens Health (Larchmt), 2010. **19**(8): p. 1441-7.

35. Neuzil, K.M., et al., *Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial.* Jama, 2011. **305**(14): p. 1424-31.

36. Lamontagne, D.S., et al., *Immunogenicity of Quadrivalent HPV Vaccine Among Girls 11 to 13 Years of Age Vaccinated Using Alternative Dosing Schedules: Results 29 to 32 Months After Third Dose.* J Infect Dis, 2013. **208**(8): p. 1325-34.

Appendix 2:

Results from non-systematic review of the data from observational studies

Data available on schedule comparisons from observational studies in the literature and from studies presented at the WHO Ad-hoc Expert Consultation were summarized by the WHO Secretariat.

Contents

Evidence on the effect of fewer than 3 doses of HPV vaccine on important outcomes: Data from observational studies

Nine observational studies providing information on vaccine effectiveness among recipients of fewer than 3 doses were identified. Eight studies were conducted in industrialized countries and one was conducted in a low-income country. Table 1 provides an overview of the studies presented and identified.

Table 1. Overview of observational studies providing information on effect of fewer than 3 doses of HPV vaccines.

First author, year/ vaccine	Age group, year*	Comparisons	Outcomes reported
Gertig, 2013[2] Quadrivalent	≤ 17	unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	any high grade histological abnormalities
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN3/AIS
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN2
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	CIN1
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose 2 dose 1 or 2 doses complete	any high grade cytological abnormalities
		unvaccinated vaccinated (unadjusted) vaccinated (adjusted) 1 dose	any low grade cytological abnormalities
Garland, 2013[4] Quadrivalent	born after 30 June 1981 (of vaccine eligible age ≤ 26 in 2007)	No doses + Vaccinated	CIN3+/AIS
	18-25		HPV infection
Blomberg, 2013[5] Quadrivalent	born 1995-1996 born 1993-1994 born 1991-1992 born 1989-1990	Vaccinated (at least one dose)	Risk of genital warts
Squarzon, 2013[1] Quadrivalent	11-13	3 doses	GMC
Pollock, 2013[11] Quadrivalent	Women attending first cervical smear		CIN3

[1] Squarzon, L. et al., Evaluation of neutralizing and cross-neutralizing antibodies induced by HPV prophylactic vaccines: an independent study. Eurogin 2013

First author, year/ vaccine	Age group, year*	Comparisons	Outcomes reported
Leval, 2013[5] Quadrivalent	<20 (10-44) 10-13 (14-16) (17-19) (20-22) (23-26) (>26) <20 (10-44) 10-13 (14-16) (17-19) (20-22) (23-26) (>26)	Vaccinated vs not fully vaccinated	Genital warts incidence
Herweijer, 2013[6 7] Quadrivalent	10-16 17-19 10-19 10-16 17-19 10-19	3 vs 2 doses	Genital warts incidence
Safaeian, 2012[10 9] Bivalent	18-25	1 vs 2 vs 3 doses	GMCs - HPV16 GMCs- HPV18
Crowe, 2014[3] Quadrivalent	12-26 years (in 2007)	Vaccinated (1, 2, or 3 doses) vs unvaccinated	Exposure odds ratio Vaccine effectiveness

Quadrivalent vaccine

In Australia, this retrospective cohort linked data from the Victorian Cervical Cytology Registry (VCCR) and the National HPV Vaccination Program Register (NHVPR) and evaluated the effectiveness of the HPV vaccine against cervical abnormalities in a screening population of women eligible for vaccination in the school based cohorts (aged 17 or younger in 2007)[2]. The retrospective cohort was constructed of women aged 17 or younger in 2007 who had a Pap test recorded on the VCCR during the study period, 1 April 2007 (the date the HPV vaccination program commenced) to 31 December 2011. Women were counted as at risk of a diagnosis of a cervical abnormality from the time they commenced cervical screening, and were entered into the cohort at their first Pap test (or on 1 April 2007 if their first Pap test was prior to that time). Unvaccinated women were those who had no doses of HPV vaccine recorded on the NHVPR; vaccinated women were those who received any doses of HPV vaccine. Average follow up was 4.8 years. Women were 17 years or younger in 2007 and had a Pap test recorded during the study period (n=39,000). Censoring occurred at the date of outcome of interest, date of death, hysterectomy or end of study period. Vaccine effectiveness (VE) and hazard ratios (HR) for cervical abnormalities by vaccination status between 1 April 2007 and 31 December 2011 were calculated using proportional hazards regression. The analysis included 24,871women aged between 12 and 17 years who were vaccinated against HPV had commenced cervical screening. Of these women, 21,151 (85.0%) were completely vaccinated and 3,690 women had received one or two doses of vaccine. There were 14,085 unvaccinated women of the same age who had commenced cervical screening. The follow-up period was a maximum of 4.8 years with an average of 1.5 years for both vaccinated women and unvaccinated women. A lower risk of any histologically confirmed HG cervical abnormality was observed for vaccinated women (any dose) compared with unvaccinated women with a hazard ratio of 0.72 (95% CI 0.58 to 0.91), after adjusting for age at first screening, SES and remoteness. This effect was strongest for completely vaccinated women; there was no significant reduction among those partially vaccinated, but the number of outcomes was small. There was a reduced risk of LG cytological abnormalities for women who received one or two doses of vaccine HR 0.66 (95%

[2] Gertig, D.M., et al., Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med, 2013. 11(1): p. 227

CI 0.60 to 0.72) compared with unvaccinated women. Vaccine effectiveness (VE), adjusted for remoteness, SES and age at first Pap test, was highest for CIN3/AIS at 47.5% (95% CI 22.7 to 64.4) for women who were completely vaccinated (compared to no doses), and was slightly lower for women who received any dose of vaccine 36.4% (95% CI 9.8 to 55.1). Methodological issues in relation to less than 3 doses may include misclassification of 2 doses (3?); assignment of dose status – time varying vs final dose; residual confounding – those who receive 2 doses in the real world may be different from those who complete the course and censoring of histological outcomes.

A case control study measured the effectiveness of the quadrivalent HPV vaccine against cervical abnormalities four years after implementation of a nationally funded vaccination programme in Queensland, Australia.[3] Participants were women eligible for free vaccination (aged 12-26 years in 2007) and attending for their first cervical smear test between April 2007 and March 2011. High grade cases were women with histologically confirmed high grade cervical abnormalities (n=1062) and "other cases" were women with any other abnormality at cytology or histology (n=10 887). Controls were women with normal cytology (n=96 404).The adjusted odds ratio for exposure to three doses of HPV vaccine compared with no vaccine was 0.54 (95% confidence interval 0.43 to 0.67) for high grade cases and 0.66 (95% CI 0.62 to 0.70) for other cases compared with controls with normal cytology, equating to vaccine effectiveness of 46% and 34%, respectively. The adjusted exposure odds ratios for two vaccine doses were 0.79 (95% CI 0.64 to 0.98) for high grade cases and 0.79 (95% CI 0.74 to 0.85) for other cases, equating to vaccine effectiveness of 21%.

A cross-sectional study -the Vaccine Against Cervical Cancer Impact and Effectiveness (VACCINE)- which focused on HPV vaccine-related infection and disease (CIN3) outcome, began in 2011, in Victoria, Australia.[4] VACCINE consisted of 2 sub-studies (A and B). Sub-study A involved Facebook recruitment of 1500 young women 18-25 years to undertake a questionnaire on line, and send a self-collected vaginal swab for HPV detection and genotyping. Sub-study B is recruiting 500 cases of CIN3/ACIS biopsies from women born after the 30th of June 1981 (of vaccine eligible age of ≤ 26 in 2007). Laser microdissection is being employed to attribute single HPV genotypes to separate CIN3 lesions. In an interim analysis of 395 subjects for sub-study A, the prevalence of HPV16 was only 1.6% (95%CI 0.6 to3.5%) and for any high risk HPV type was 14.4% (95% CI 11.0 to18.4%). No HPV18 was detected. Eighty one percent of the cohort was fully vaccinated.

Using individual-level data from the entire Swedish population a study assessed genital warts (GW) incidence after on-demand vaccination with quadrivalent HPV vaccine[5]. An open cohort of girls and women aged 10 to 44 years living in Sweden between 2006 and 2010 (N > 2.2 million) was linked to multiple population registers to identify incident GW in relation to HPV vaccination. For vaccine effectiveness, incidence rate ratios of GW were estimated using time-to-event analyses with adjustment for attained age and parental education level, stratifying on age at first vaccination. A total of 124 000 girls and women were vaccinated between 2006 and 2010. Girls and women with at least one university-educated parent were 15 times more likely to be vaccinated before age 20 years than girls and women whose parents did not complete high school (relative risk ratio = 15.45, 95% CI14.65 to 16.30). Among those aged older than 20 years, GW rates declined among the unvaccinated, suggesting that HPV vaccines were preferentially used by women at high risk of GW.

---

[3] Crowe, E., et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014; 348:g1458. doi: http://dx.doi.org/10.1136/bmj.g1458 (Published 4 March 2014).

[4] Garland, S.M., et al. Measures of vaccine effectiveness. Abstract no. SS 22-7 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy

[5] Leval, A., et al., Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst, 2013. 105(7): p. 469-74.

Vaccination effectiveness (VE) was 76% (95% CI 73 to 79) among those who received three doses of the vaccine with their first dose before age 20 years. Vaccine effectiveness was highest in girls vaccinated before age 14 years (VE 93%, 95% CI 73 to 98).

In Sweden, a population based study to examine the association between quadrivalent HPV vaccination and first occurrence of condyloma in relation to vaccine dose was conducted.[6, 7] An open cohort of all females aged 10 to 24 years living in Sweden (n = 1 045 165) was followed up between 2006 and 2010 for HPV vaccination and first occurrence of condyloma using the Swedish nationwide population-based health data registers. Incidence rate ratios (IRRs) and incidence rate differences (IRDs) of condyloma were estimated using Poisson regression with vaccine dose as a time-dependent exposure, adjusting for attained age and parental education, and stratified on age at first vaccination. To account for prevalent infections, models included a buffer period of delayed case counting. A total of 20 383 incident cases of condyloma were identified during follow-up, including 322 cases after receipt of at least 1 dose of the vaccine. For individuals aged 10 to 16 years at first vaccination, receipt of 3 doses was associated with an IRR of 0.18 (95%CI, 0.15 to 0.22) for condyloma, whereas receipt of 2 doses was associated with an IRR of 0.29 (95%CI, 0.21 to 0.40). One dose was associated with an IRR of 0.31 (95%CI, 0.20 to 0.49), which corresponds to an IRD of 384 cases (95%CI, 305 to 464) per 100 000 person-years, compared with no vaccination. The corresponding IRDs for 2 doses were 400 cases (95%CI, 346 to 454) and for 3 doses, 459 cases (95%CI, 437 to 482). The number of prevented cases between 3 and 2 doses was 59 (95%CI, 2 to117) per 100 000 person-years.

Although maximum reduction in condyloma risk was seen after receipt of 3 doses of quadrivalent HPV vaccine, receipt of 1 or 2 vaccine doses was also associated with a considerable reduction in condyloma risk. The implications of these findings for the relationship between number of vaccine doses and cervical cancer risk require further investigation, especially regarding the interval between the first and the 2nd dose. Substantial protection was found with less than three doses. The additional protection provided with the 3rd dose, especially in the 10-16 group, was limited and sensitive to buffer period length. Using a longer buffer period (>5 months) to account for prevalent infections resulted in no significant effectiveness differences between 2 and 3 doses. The study had limited power to assess dose effectiveness in girls first-vaccinated at ages 10-13.

A cohort study aiming to use individual information on HPV vaccination status to assess the effect on risk of GWs was conducted in Denmark.[8] Population-based registries were used to identify all girls in the birth cohorts 1989–1999 in Denmark, and information about HPV vaccination was obtained for the period 2006–2012. The cohort was linked to incident cases of GWs, and vaccinated and unvaccinated girls were compared using Cox proportional hazards models. A total of 248 403 girls were vaccinated. The relative risk of GWs among girls who had received at least 1 dose of vaccine compared with unvaccinated girls was 0.12, 0.22, 0.25, and 0.62 for those born in 1995–1996, 1993–1994, 1991–1992, and 1989–1990, respectively (*P* for trend <.0001). No GWs occurred among vaccinated girls in the youngest birth cohort (1997–1999).

[6] Herweijer, E., Association of Varying Number of Doses of Quadrivalent Human Papillomavirus Vaccine With Incidence of Condyloma. JAMA. 2014;311(6):597-603. doi:10.1001/jama.2014.95.

[7] Herweijer, E., et al. Dose effectiveness of quadrivalent human papillomavirus vaccine: A national cohort study. Abstract no. OC 6-6 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

[8] Blomberg, M., et al., Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated girls in Denmark. Clin Infect Dis, 2013. 57(7): p. 929-34.

Bivalent vaccine

Young girls who participated in an HPV vaccine demonstration project in Uganda (2008-2009) were eligible for this study.[9,10] The study included all girls who had received one or two HPV vaccine doses (at whatever interval), and a subset from those who had received all three doses. In addition inclusion criteria required at least 24 months since receipt of their last vaccine dose (1 dose=37; 2 doses=144, 3 doses=195). HPV16 and HPV18 specific antibody levels were measured using an enzyme linked immunoassay (ELISA). Non-inferiority was assumed if the lower bound of the multiplicity-adjusted confidence interval (CI) of the type-specific geometric mean titer (GMT) ratio was greater than 0.5. The ratio of HPV16 and HPV18 GMTs comparing 2 dose to 3 dose groups were 0.51 (97.5%CI=0.37-0.69), and 0.69 (97.5%CI=0.50-0.96). HPV16 and HPV18 antibody GMTs were higher in all dose groups compared to naturally infected women from Costa Rica HPV Vaccine Trial (CVT) (HPV16 natural infection=37 vs. HPV16 1 dose=234, HPV16 2 doses=812, HPV16 3 doses=1608; p-value<0.001). Anti-HPV18 GMTs for 1, 2, 3, dose groups were 85, 274, and 396, respectively, compared to 19 among naturally infected (p-value for Uganda 1 dose vs. CVT<0.001).

An observational study using the data from a programme of longitudinal HPV surveillance was conducted in Scotland.[11] Key elements of surveillance were yearly sampling and HPV genotyping of women attending for their first smear and the monitoring of high-grade lesion prevalence through interrogation of national databases. As age at screening debut is currently 20 in Scotland, this data was used to determine the impact of a national immunisation programme on rates of HPV infection and HPV associated disease. Liquid-based cytology (LBC) samples from women attending their first cervical smear were genotyped for HPV and data linkage enabled HPV prevalence to be stratified by immunisation status. In addition, analysis included data from the National Colposcopy Clinical Information and Audit System (NCCIAS), a national colposcopy database that contains data on referral cytology, interventions and histology results associated with any colposcopy visit. While the vaccine was not associated with a reduction in low-grade cervical abnormalities, there was a statistically significant reduction in CIN3 diagnoses associated with vaccination status.

Summary of findings from observational studies providing information on effect of fewer than 3 doses of HPV vaccines

These observational studies reporting vaccine effectiveness after 2 versus 3 doses are based on a prime, prime, boost schedule. Contrastingly, a prime-boost alternative schedule may require a longer interval between doses. When interpreting effectiveness of 2 dose schedules, it is important to take into account that a 2-dose schedule must include at least 4 months before the 2nd dose to fulfill the criteria of a prime-boost (and not a prime-prime) schedule.

[9] http://www.childsurvival.net/?content=com_articles&artid=1666.

[10] Safaeien, M. Immunogenicity of the bivalent HPV vaccine among partially vaccinated young girls in Uganda. in 28th International Papillomavirus Conference & Clinical and Public Health Workshops, Abstract book page no. 326. 2012: San Juan, Puerto Rico.

[11] Pollock, K., et al. Early effect of the HPV bivalent vaccine on high-risk HPV prevalence and high-grade cervical abnormalities in Scotland. Abstract no. OC 6-2 in Eurogin 2013 International Multidisciplinary Congress. 2013: Florence, Italy.

Table 2. Summary of findings from observational studies providing information on effect of fewer than 3 doses of HPV vaccines

Country	First author, year, ref	Comparison	Outcomes reported	Estimate type	Estimated Value	lower limit	upper limit
Australia	Gertig, 2013[2]	unvaccinated	any high grade histological abnormalities	Hazard Ratio	1		
		vaccinated (unadjusted)			0.76	0.61	0.95
		vaccinated (adjusted)			0.72	0.58	0.91
		1 dose			1.47	0.97	2.23
		2 dose			1.02	0.68	1.53
		1 or 2 doses			1.2	0.88	1.65
		complete			0.61	0.48	0.78
		unvaccinated	CIN3/AIS		1		
		vaccinated (unadjusted)			0.68	0.48	0.95
		vaccinated (adjusted)			0.64	0.45	0.9
		1 dose			1.4	0.75	2.61
		2 dose			0.87	0.46	1.67
		1 or 2 doses			1.09	0.67	1.76
		complete			0.53	0.36	0.77
		unvaccinated	CIN2		1		
		vaccinated (unadjusted)			0.81	0.61	1.06
		vaccinated (adjusted)			0.78	0.59	1.03
		1 dose			1.29	0.76	2.2
		2 dose			0.99	0.59	1.64
		1 or 2 doses			1.11	0.75	1.66
		complete			0.7	0.52	0.94
		unvaccinated	CIN1		1		
		vaccinated (unadjusted)			0.86	0.7	1.05
		vaccinated (adjusted)			0.83	0.68	1.02
		1 dose			0.89	0.56	1.41
		2 dose			0.9	0.61	1.33
		1 or 2 doses			0.9	0.65	1.23
		complete			0.82	0.66	1.01
		unvaccinated	any high grade cytological abnormalities		1		
		vaccinated (unadjusted)			0.77	0.67	0.89
		vaccinated (adjusted)			0.75	0.65	0.87
		1 dose			0.85	0.62	1.17
		2 dose			0.95	0.73	1.23
		1 or 2 doses			0.91	0.73	1.13
		complete			0.71	0.61	0.83
		unvaccinated	any low grade cytological abnormalities		1		
		vaccinated (unadjusted)			0.77	0.73	0.82
		vaccinated (adjusted)			0.76	0.72	0.8
		1 dose			0.67	0.59	0.76
Australia	Garland, 2013[4]	No doses	CIN3+/AIS HPV infection	Prevalence of HPV16	1.60%	0.6	3.5
		±Vaccinated		Prevalence of any risk HPV type	14.40%	11	18.4
Australia	Crowe 2014[3]	Vaccinated (1, 2, or 3 doses) vs unvaccinated	Cervical abnormalities – high grade cases	Exposure odds ratio 3 vs 0 doses	0.54	0.43	0.67
			Cervical abnormalities – other grade cases	Exposure odds ratio 3 vs 0 doses	0.66	0.62	0.70
			Cervical abnormalities – high grade cases	Exposure odds ratio 2 vs 0 doses	0.79	0.64	0.98
			Cervical abnormalities – other grade cases	Exposure odds ratio 2 vs 0 doses	0.79	0.74	0.85
Denmark[8]	Blomberg, 2013[8]	Vaccinated born 1995-1996	Risk of genital warts vaccinated (at least one dose) vs unvaccinated	relative risk of vaccinated vs unvaccinated	0.12		
		Vaccinated born 1993-1994			0.22		
		Vaccinated born 1991-1992			0.25		
		Vaccinated born 1989-1990			0.62		

Country	First author, year, ref	Comparison	Outcomes reported	Estimate type	Estimated Value	lower limit	upper limit
Sweden	Leval, 2013[5]	< 20 y	Genital warts incidence vaccinated vs not fully vaccinated	Incidence rate ratios	0.24	0.21	0.27
		10-44 y			0.27	0.24	0.3
		10-13 y			0.07	0.02	0.27
		14-16 y			0.2	0.17	0.25
		17-19 y			0.29	0.24	0.35
		20-22 y			0.52	0.35	0.78
		23-26 y			0.79	0.47	1.33
		≥ 27 y			2.32	0.87	6.18
		< 20 y		Effectiveness %	76	73	79
		10-44 y			73	70	76
		10-13 y			93	73	98
		14-16 y			80	75	83
		17-19 y			71	65	76
		20-22 y			48	22	65
		23-26 y			21	<0	53
		≥ 27 y			<0	<0	13
Sweden	Herweijer, 2013[6 7]	3 vs 2 d in 10-16 y	prevalence of HPV 16	Incidence rate ratios	0.63	0.43	0.93
		3 vs 2 d in 17-19 y			0.66	0.45	0.95
		3 vs 2 d in 10-19 y			0.63	0.48	0.82
		3 vs 2 d in 10-16 y		Incidence rate difference	59	2	117
		3 vs 2 d in 17-19 y			67	3	132
		3 vs 2 d in 10-19 y			66	23	109
Uganda	Safaeian, 2012[9 10]	2 vs 3 doses	GMCs - HPV16	GMT ratios	0.51	0.37	0.69
			GMCs- HPV18		0.69	0.5	0.96
* Age groups in brackets are outside range defined in PICO ; ± vaccinated schedule not reported assume licensed schedule							