Strategic Advisory Group of Experts (SAGE) on Immunization

Working Group on potential contribution of Human Papillomavirus (HPV) vaccines and immunization towards cervical cancer elimination

Background Document and Report to SAGE

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EXECUTIVE SUMMARY

Objectives of the 6-7 June 2019 meeting of Working Group on HPV immunization:

1. To discuss preliminary outcomes of updated systematic reviews and meta-analyses on one-dose schedule and interval between doses of HPV vaccine, and all related evidence;
2. To discuss vaccine allocation strategy(ies) to achieve more equitable access to HPV vaccines; and
3. To review the potential effect on HPV infection, disease and access to HPV vaccine in the short and mid-term of various schedule and vaccine allocation strategies.

Questions considered by the Working Group:

1. What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines?
2. What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine and different intervals between the first and second doses of HPV vaccine? And what are the risks of bias of these studies?
3. What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could the enhanced HPV vaccine supply allocation be?
4. In light of the above conclusions and evidence, how should HPV vaccine introduction be prioritized with respect to impact and feasibility?

Summary recommendations:

The primary target population for HPV vaccination should continue to be girls aged 9-14 years, prior to becoming sexually active, with a two-dose schedule.

A 3-dose schedule recommendation for girls ⩾15 years of age, including for those younger than 15 years known to be immunocompromised and/or HIV-infected (regardless of whether they are receiving antiretroviral therapy) remains valid.

Current evidence suggests that from the public health perspective, the three licensed HPV vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer. Countries should therefore consider all product options available to ensure swift start of HPV vaccination programmes.

Concerned by the global situation of constrained HPV vaccine supply, the Working Group proposes the additional following recommendations:

1. The Working Group encourages SAGE to make a strong statement about the need for a more equitable global allocation of limited HPV vaccine supply across countries based on public health considerations and requests WHO to take a more active role in facilitating such allocation.
2. The Working Group requests SAGE to encourage manufacturers to expand the availability of HPV vaccines to girls in low- and middle-income where the burden of cervical cancer is the greatest.
3. The recommended primary target of HPV vaccine remains girls aged 9-14 years with a 2-dose schedule and at least 6 months interval between doses.
4. In the context of supply constraint, introduction of multiple age-cohorts vaccination, gender-neutral and older age group vaccination strategies in any country should be temporarily postponed until all countries have been able to introduce HPV vaccination in at least one age-cohort (i.e. a single year each cohort) of the WHO recommended primary target population of 9-14-year-old girls.

5. Countries introducing HPV vaccine should consider initially targeting one older cohort of girls (e.g. 13 or 14 years old) as this strategy will retain the maximum disease impact of HPV vaccination in terms of cervical cancer cases prevented.

6. Countries that have already introduced HPV vaccine and face an imminent vaccine supply shortage can consider a "1+1" schedule with an extended interval for the administration of the second dose of up to 3-5 years for younger girls (e.g. 9 or 10 years of age).

7. For countries that experience complete stock-outs of HPV vaccine, efforts should be made to ensure that eligible girls who were missed are vaccinated as soon as possible and before they turn 15 years old.

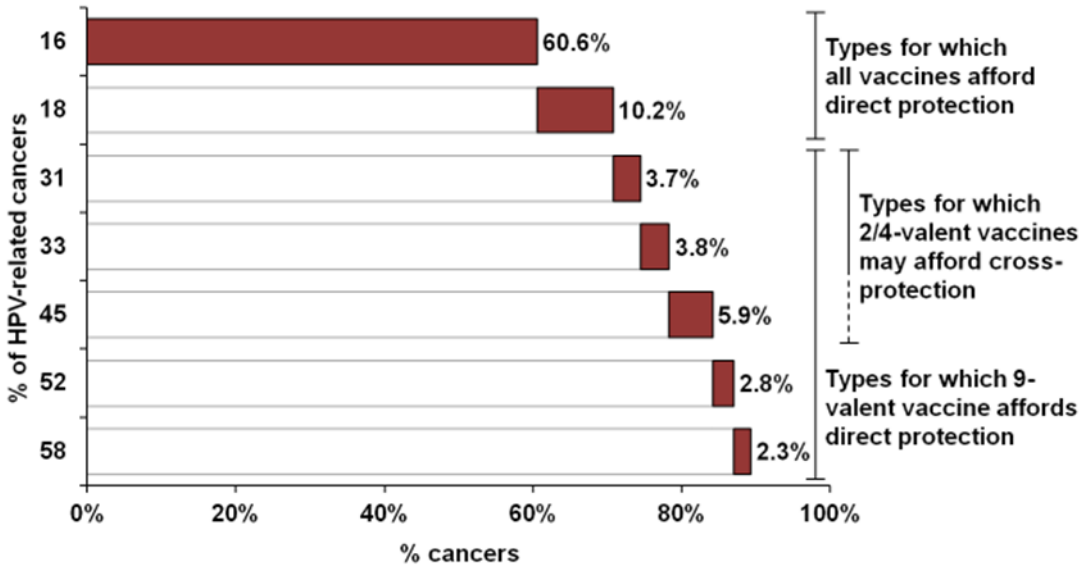
The Working Group welcomes the ongoing trials assessing single-dose schedules and anticipate that they will be very useful to inform future policy recommendations.

BACKGROUND

In the meeting of SAGE in October 2018[1], SAGE affirmed that HPV vaccination is the most critical intervention for eliminating cervical cancer. Introduction of HPV vaccine should be prioritized in all countries but especially in countries with the highest cervical cancer rates. The SAGE Working Group on HPV immunization held a meeting in Menthon-Saint-Bernard, France on 6-7 June 2019. The Terms of Reference for the Working Group, list of participants with Working Group membership and meeting agenda are provided in Appendices.

All three licensed HPV vaccines – bivalent (HPV genotypes 16/18), quadrivalent (HPV 6/11/16/18) and nonavalent (HPV 6/11/16/18/31/33/45/52/58) – have excellent safety, efficacy, immunogenicity and effectiveness profiles. The risk attribution of HPV 16/18 in women with cervical cancer is approximately 70%[2] Fig 1).

Figure 1. Relative contribution of different viral types to cervical cancer – World, 2012



Serrano et al, 2015

The (Draft) *Global Strategy Towards the Elimination of Cervical Cancer as a Public Health Problem*[3] calls for a comprehensive, population-based approach to put all countries on the path to the elimination of cervical cancer as a public health problem

[1] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and recommendations, Dec 2018. Weekly epidemiological record 2018;49(93):661-680.
https://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf

[2] Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related
Diseases in the World. Summary Report 17 June 2019. [Accessed on 14 Aug 2019]

[3] https://www.who.int/cancer/cervical-cancer/cervical-cancer-elimination-strategy

within the century. The strategy proposes an approach that will enable countries to reach 2030 global targets for key interventions that, in turn, will lead to elimination of cervical cancer as a public health problem. The proposed targets for 2030 are: (i) 90% of girls being fully vaccinated with HPV vaccine by 15 years of age; (ii) 70% of women being screened with a high-precision test[4] at 35 and 45 years of age; and; (iii) 90% of women identified with precancer lesions or invasive cervical cancer receiving treatment.

As of June 2019, 96 countries (49%) have introduced HPV vaccines in the national immunization programmes or in part of the countries. Currently, an estimated 30% of girls aged 9-14 years globally live in countries that have introduced the HPV vaccine. However, preliminary data on WHO estimates of the HPV vaccine coverage show that the average HPV vaccine coverage in countries with available data is 64% for the first dose and 52% for the second dose[5]. Since 2018, limited number of doses in supply has affected HPV vaccine introductions and introduction plans across the global. However, as noted below there are several other known barriers to vaccine introduction and coverage. In 2019, all planned Gavi-supported HPV vaccine introductions are going ahead for the routine recommended cohorts. However, the multiple age-cohorts vaccination (MACs) have been postponed to later dates in the majority of these countries. Introductions in non-Gavi Middle Income Countries are also constrained by limited vaccine supply. Concerned by constrained HPV vaccine supply, in October 2018 SAGE called for a comprehensive evaluation of options for the best use and allocation of the limited vaccine supply[6]. In response to this recommendation, the SAGE Working Group on HPV Immunization reviewed the data on vaccination barriers and immunization schedules, reviewed modelling results on vaccination strategies and assessed options to achieve more equitable allocation of HPV vaccines in the context of supply constraint.

[4] A WHO recommended high-precision test which would have performance characteristics similar to or better than a clinically approved HPV DNA test. In the future, however, new technologies may be available.
[5] WHO IVB database, preliminary results, as of May 2019
[6] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and recommendations, Dec 2018. Weekly epidemiological record 2018;49(93):661-680.
https://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf

SUMMARIES OF EVIDENCE REVIEWED

Barriers to access to HPV vaccines

Barriers to access HPV vaccines impact at two levels: those preventing the introduction of HPV vaccine in national immunization programmes and those that prevent reaching and maintaining high coverage after introduction.

Barriers to HPV vaccine introduction

Barriers to HPV vaccine introduction are numerous and include limited supply of HPV vaccines, affordability of HPV vaccination due to the high vaccine price and vaccine delivery cost, competing priorities (versus HPV vaccination) in countries and vaccine hesitancy.

HPV vaccine affordability is a major barrier especially in non-Gavi middle-income countries (MICs). The reported median price for self-procuring non-Gavi MICs for bivalent and quadrivalent HPV vaccines are approximately three times the Gavi (UNICEF Supply Division) price (median price = US$4.50) about 20% higher than the PAHO Revolving Fund price (median price = US$9.58). Nevertheless, the price of the vaccine for this market segment can vary greatly from US$ 7.64 to US$ 88.54 per dose.[7] Among countries with data available, the costs of vaccine delivery, excluding vaccine procurement costs, range from US$0.4-US$20 per fully immunized person[8].

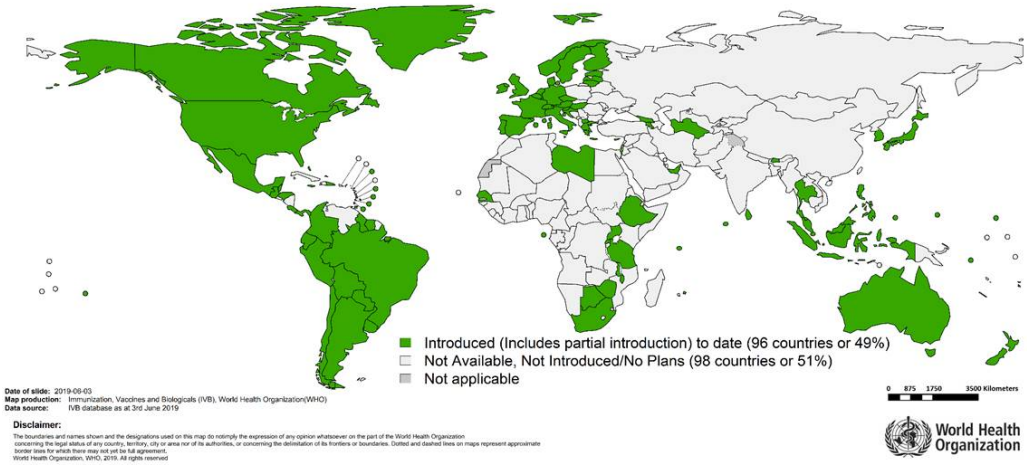
In addition, there are technical barriers such as establishing the burden of HPV disease and cervical cancer; political barriers such as decision-makers prioritization of HPV vaccine and willingness to pay.

Barriers to low coverage of HPV vaccination

The low coverage of HPV vaccination in some countries is a result of a combination of factors: the quality and comprehensiveness of the social mobilization and overall introduction planning, the choice and sustainability of vaccine delivery strategies, vaccine acceptance and hesitancy in the population and health professionals, equity in accessibility of the vaccine (e.g. out of school girls or those in private schools), and, in countries with insurance systems the reimbursement process and eventual out-of-pocket contributions.

[8] WHO Cervical Cancer Prevention and Control Costing (C4P) Tool

Figure 2. Countries with HPV vaccine introduced in national immunization programme, JUNE 2019



HPV vaccination schedules - single dose schedule

Systematic review of evidence - COCHRANE

A systematic review[9] conducted by Cochrane Response updated and expanded upon a previous review for the WHO Initiative for Vaccine Research. The data are current to 29 February 2019 when the most recent literature search was performed.

Randomized controlled trials (RCTs) and observational studies capable of providing evidence on the efficacy, effectiveness or immunogenicity following one dose of HPV vaccine in females and males aged ≥ 9 years were eligible to be included.

The review included studies of all licensed (and under clinical evaluation) HPV vaccines (bivalent, quadrivalent, and nonavalent).

The systematic review considered studies that provided data on one-dose versus no HPV vaccination/placebo/control vaccine, one-dose versus two doses, or one-dose versus three doses of the licensed HPV vaccines.

The outcomes of interest were:

- Immunological: seroconversion or seropositivity, geometric mean titres (GMT) of HPV antibodies
- Clinical: including, but not limited to cervical intraepithelial neoplasia (CIN) grade 3+, CIN2+, histological and cytological abnormalities, anogenital warts, and HPV infection

In part due to the unique aspects of HPV immunogenicity and high levels of efficacy no immune correlate has been identified for HPV vaccination. Serum neutralizing antibodies are used to measure vaccine response, but their role as a correlate has not been verified.[10] The minimum antibody level required for clinical protection is unknown.

The risk of bias was assessed for all included studies. Biases due to confounding, selection bias, information bias, and reporting bias were critically assessed in observational studies. Confounding domains in the minimal adjustment set included age, ethnicity/cultural context, socioeconomic status, peer group, directive sexual education and mass media, contraception, history of sexually transmitted infection and Pap testing, and vaccination delivery setting.

[9] 'Effectiveness and immunogenicity of one dose of HPV vaccine compared with no vaccination, two doses, or three doses' presented by Cochrane Response on the SAGE Working Group on HPV immunization meeting on 6-7 June 2019.
[10] Turner T.B., Huh W.K. HPV vaccines: Translating immunogenicity into efficacy. Human Vaccines and Immunotherapeutics 2016 Jun, 12(6): 1403-1405.

Randomised evidence

The systematic review did not identify any randomized comparisons from RCTs that directly assessed the single-dose HPV vaccine schedule.

Table 1. Studies included in systematic review on single-dose schedule

Comparison	Vaccine type	Endpoints	Location (unadjusted estimates in grey)
One dose versus no vaccination	Bivalent	Immunogenicity (1 study)	Costa Rica1
		CIN, etc. (3 studies)	Scotland2, Scotland3, Scotland6
		HPV infection (5 studies)	Costa Rica1, CVT/PATRICIA, Scotland1, Scotland4, Scotland5
	Quadrivalent	Immunogenicity (1 study)	Fiji1
		CIN, cytology, etc. (8 studies)	Australia1, Australia2, Australia3, Australia 4, Canada2, Denmark3, Denmark/Sweden1, USA1, USA9, USA13
		Genital warts (9 studies)	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA10, USA11
		HPV infection (1 study)	India1
One dose versus two doses	Bivalent	Immunogenicity (2 studies)	Costa Rica1, Uganda1
		CIN, etc. (2 studies)	Scotland2, Scotland3
		HPV infection (5 studies)	Costa Rica1, CVT/PATRICIA, Scotland1, Scotland4, Scotland5
	Quadrivalent	Immunogenicity (3 studies)	Fiji1, India1, USA16
		CIN, cytology, etc. (8 studies)	Australia1, Australia2, Australia3, Australia4, Canada2, Denmark3, USA1, USA9
		Genital warts (8 studies)	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11
		HPV infection (1 study)	India1
One dose versus three doses	Bivalent	Immunogenicity (2 studies)	Costa Rica1, Uganda1
		CIN, etc. (2 studies)	Scotland2, Scotland3
		HPV infection (5 studies)	Costa Rica1, CVT/PATRICIA, Scotland1, Scotland4, Scotland5
	Quadrivalent	Immunogenicity (3 studies)	Fiji1, India1, USA16
		CIN, cytology, etc. (8 studies)	Australia1, Australia2, Australia3, Australia4, Canada2, Denmark3, USA1, USA9
		Genital warts (8 studies)	Belgium2, Canada3, Denmark2, Spain2, Sweden1, USA2, USA6, USA11
		HPV infection (1 study)	India1, Switzerland1, USA12, USA14, USA15

Evidence from observational studies

The systematic review identified 35 studies: 32 observational cohort studies, of which three were post-hoc analyses of RCTs, and three case-control studies.

The studies were carried out in 21 countries; 10 studies evaluated the bivalent vaccine, 24 studies the quadrivalent vaccine, and one study evaluated both quadrivalent and nonavalent vaccines.

Only two studies were identified which assessed the efficacy of one dose of HPV vaccine in males (USA11, USA12). USA11 included both males (23% of cohort) and females but did not report results separately by sex. USA12 reported on young men attending sexual health clinics and only provided limited data on HPV infections for this report.

The results from this systematic review should be interpreted with caution due to the moderate to serious risk of bias in the included studies. In addition, the estimates of effectiveness between one dose and two or three doses were mostly calculated using raw data reported in the studies as adjusted estimates were not available for many of these comparisons. For many outcomes there was insufficient evidence, due to a small number of participants receiving only one dose of HPV vaccine in the included studies, and only a few events of interest occurring in this group.

One dose of bivalent HPV vaccine compared with no HPV vaccine (see pages 23-26 in systematic review report)

Results from one study (Costa Rica1) showed that one dose of bivalent HPV vaccine resulted in higher HPV 16/18 GMTs (moderate certainty evidence).

One study (CVT/PATRICIA) showed fewer one-time detection of first incident HPV infections and fewer 6-month and 12-month persistent HPV infections (low to moderate certainty evidence), compared with no HPV vaccine.

Due to serious limitations in study design and imprecision, evidence on histological abnormalities and prevalent HPV infections was of very low certainty.

One dose of quadrivalent HPV vaccine compared with no HPV vaccine (see pages 26-34 in the systematic review report)

One dose of quadrivalent HPV vaccine resulted in higher HPV 6/11/16/18 GMTs and seropositivity (Fiji1, very low certainty evidence), and fewer incident HPV infections (India1, low certainty evidence), compared with no HPV vaccine.

Due to serious limitations in study design and imprecision due to few events, evidence on histological abnormalities and prevalent HPV infections was of very low certainty.

One dose compared with two doses of bivalent HPV vaccine (see pages 34-39 in the systematic review report)

Two studies (CostaRica1, Uganda1) showed that one dose of bivalent HPV vaccine resulted in lower GMTs for HPV 16/18 compared with two doses but non-inferiority

between one and two doses was inconclusive (low certainty evidence). There was little or no difference on HPV 16/18 seropositivity (low certainty evidence).

Unadjusted estimates for one-time detection of first incident HPV infections and persistent HPV infections from one study (CVT(PATRICIA) (very low to low certainty evidence) with one dose of bivalent HPV vaccines compared with two doses reported little to no difference on incident HPV 16/18 and HPV 31/33/45 infections (figure 3). There was an effect in favour of one dose for 6- and 12-month persistent HPV infections, but confidence intervals were very wide and crossed the line of no effect (Figure 4).

Figure 3 One-time incidence[11] of HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results

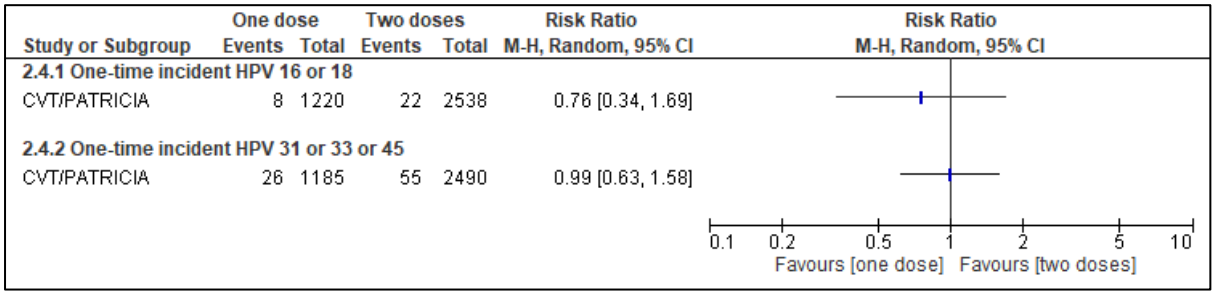
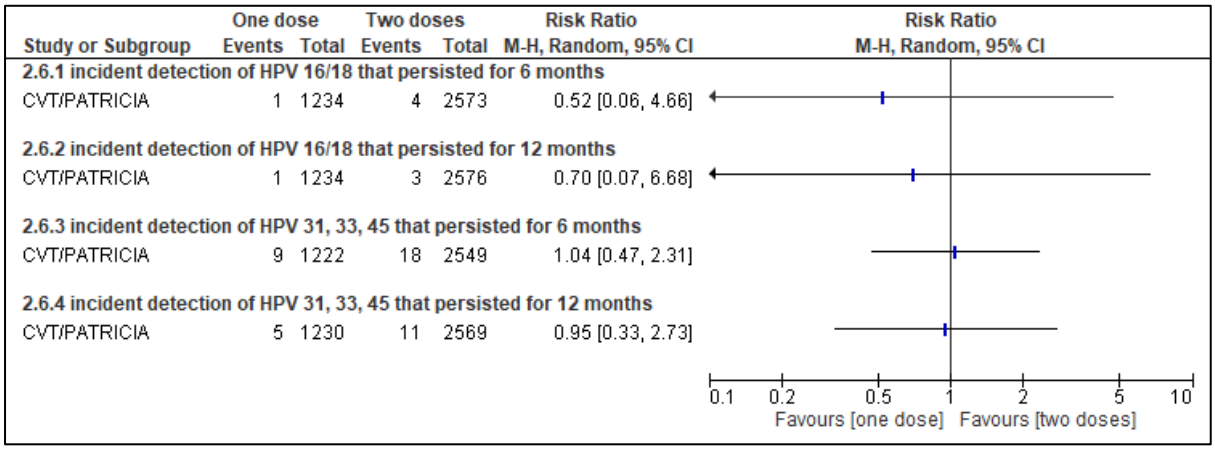


Figure 4 Persistent HPV infection for one versus two doses bivalent HPV vaccine, unadjusted results



Evidence on histological abnormalities (Scotland2, Scotland3), prevalent HPV infection (Scotland1, Scotland4, Scotland5), and 7-year cumulative HPV infections 16/18/31/33/45 infection (Costa Rica1, very low certainty evidence due to serious limitation in study design and imprecision).

None of the eight studies that compared one dose to two doses of bivalent HPV vaccine reported the use of a buffer period in the analysis, and hence a sensitivity

[11] The primary study endpoint in the CVT was one-time detection of first incident HPV infections accumulated over the follow-up phase. Women with multiple events were only counted once at the time of the first event, at which time her person-time stopped.

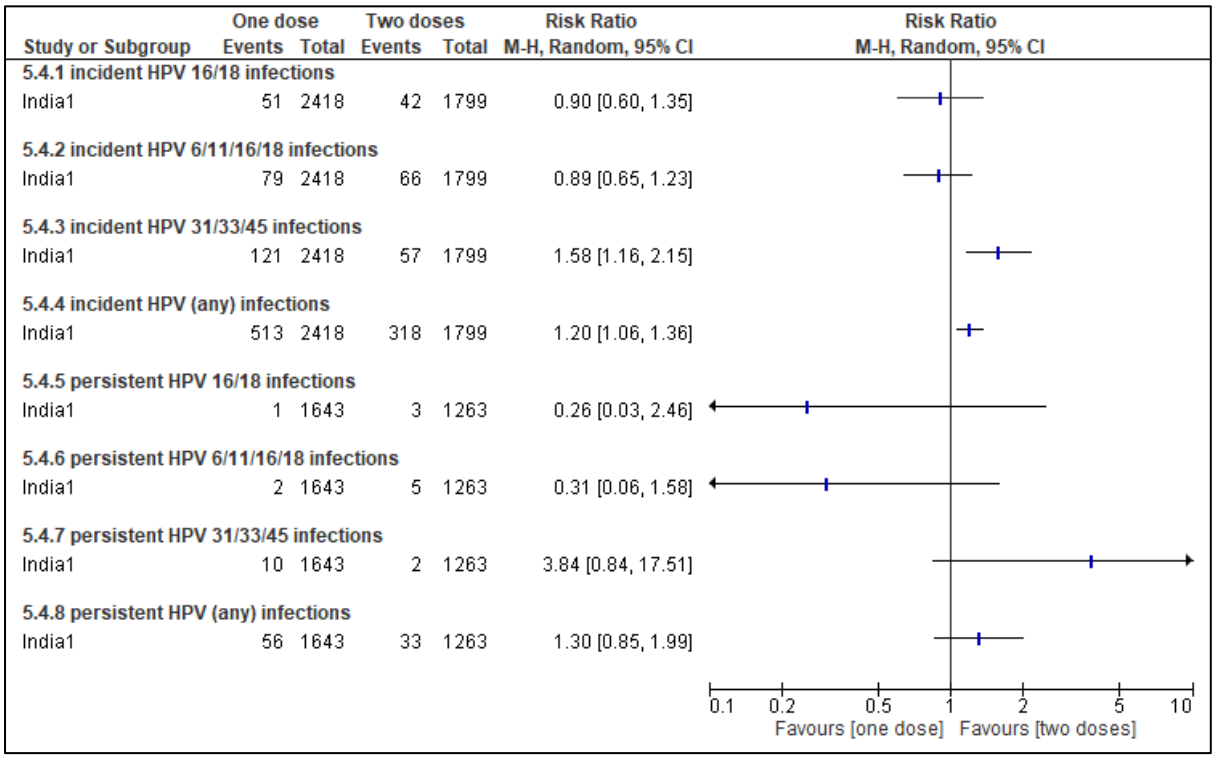
analysis on studies of bivalent HPV vaccine was not carried out. The buffer period is defined as the time between vaccination and outcome counting. Buffer periods attempt to exclude conditions caused by prevalent infection at the time of vaccination and thus deal with the bias on the impact of vaccination on new infections.

One dose compared with two doses of quadrivalent HPV vaccine (see pages 39-45 of the systematic review report)

Two studies (Fiji1, India1) showed one dose of quadrivalent HPV vaccine resulted in lower GMTs for HPV 6/11/16/18 compared with two doses but non-inferiority was inconclusive (low certainty evidence).

There was little or no difference in incident HPV16/18 infections (low certainty evidence), but more incident HPV 31/33/45 infections when one dose was compared with two doses.

Figure 5 HPV incident and persistent infection for one dose versus two doses quadrivalent vaccine at 7 years follow-up, unadjusted results.



For quadrivalent HPV vaccine, results partially adjusted for confounding from one study with moderate risk of bias (USA2) indicated little or no difference between one and two doses on incidence of genital warts and one study with serious risk of bias (Sweden1) found that two doses compared with one dose had a decreased incidence of genital warts (low certainty evidence).

Evidence on HPV 6/11/16/18 seropositivity (Fiji1, USA16) showed little to no difference in rate of seropositivity.

Two studies (Australia4, Denmark3) reported adjusted estimates for CIN2+ and CIN3+ and showed little or no difference between one and two doses of quadrivalent vaccine for these outcomes. There was insufficient evidence from six studies (Australia1, Australia2, Australia3, Australia4, Denmark3, USA9) to determine if a difference exists between one dose and two doses of HPV vaccine on CIN1 and CIN2.

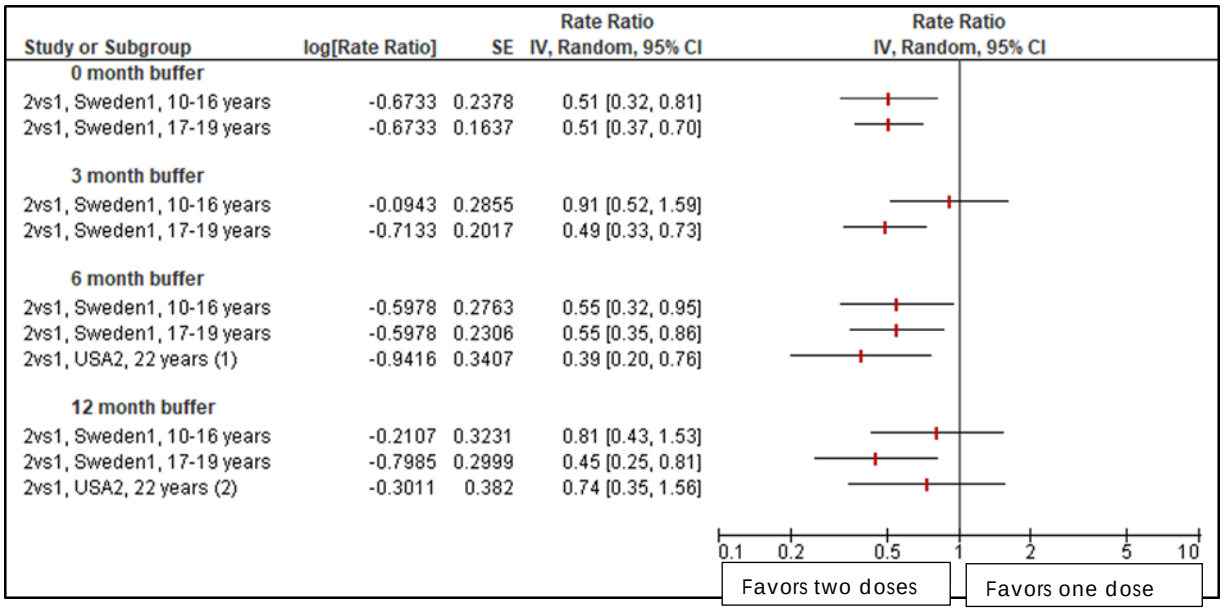
Four studies (Australia1, Australia3, Canada2, USA1) showed little to no difference between one and two doses of quadrivalent HPV vaccine on high-grade, low-grade or any abnormal cytology.

There was insufficient evidence to determine if a difference exists between one dose and two doses of quadrivalent HPV vaccine on incident HPV 16/18, HPV 6/11/16/18, HPV 31/33/45, and any HPV type infections, as well as persistent HPV 16/18, HPV 6/11/16/18, HPV 31/33/45, and any HPV type infections, due to the limited number of cases reported (very low certainty evidence due to serious limitations in study design and imprecision due to few number of events).

Sensitivity analysis of one dose HPV vaccine efficacy by risk of bias

A sensitivity analysis was performed on the included studies comparing one dose to two doses of HPV vaccine, to determine the effect of the buffer period on the effect size estimates. With no consideration of buffer period the estimates are in favour of two doses over one dose. However, with a 12-month buffer period there appears to be little or no difference between one dose and two doses for two of the estimates. For the older age group in the Sweden study (17-19 years), two doses appear to result in fewer cases of genital warts than one dose even after applying the 12-month buffer. The adjusted estimates are imprecise, with wide confidence intervals, which are likely due to few events in both groups and small sample sizes.

Figure 6 Sensitivity analysis by length of buffer period and age at first vaccine on genital warts for two doses versus one dose quadrivalent HPV vaccine, adjusted estimates



One dose compared with three doses of bivalent HPV vaccine (see pages 46-50 in the systematic review report)

Two studies (Costa Rica1, Uganda1) showed one dose of bivalent vaccine was inferior to three doses in terms of GMTs for HPV 16/18 (moderate certainty evidence).

There was little or no difference on HPV16/18 seropositivity (low certainty evidence) and one-time detection of first incident and persistent HPV infections (CVT/PATRICIA) (very low to moderate certainty evidence) with one dose compared with three doses.

Evidence on histological abnormalities (Scotland2, Scotland3), prevalent HPV infection (Scotland1, Scotland4, Scotland5), and 7-year cumulative HPV 16/18/31/33/45 infection (Costa Rica1) was of very low certainty due to serious limitations in study design and imprecision from few events.

One dose compared with three doses of quadrivalent HPV vaccine (see pages 50-56 in the systematic review report)

One dose of quadrivalent vaccine resulted in reduced GMTs for HPV 6/11/16/18 in females aged 10 to 19 years compared with three doses but non-inferiority was inconclusive (low certainty evidence). In observational studies, three doses compared with one dose had a decreased incidence of genital warts (low certainty evidence).

Single-dose HPV Vaccine Evaluation Consortium

In addition, the Single-dose HPV Vaccine Evaluation Consortium reviewed single-dose protection from non-randomized data nested in RCTs and from observational studies.

While both types of data are lower quality data than those from RCTs, the Consortium reviewers argued that in relation to the non-randomised data from post-licensure observational studies, the trials have pre-vaccination information (i.e. HPV status at time of HPV vaccination); trials contain in-depth information on covariates; virologic endpoints can be used to evaluate infection risk profile by dose group; reasons for missing doses can be known and are usually unrelated to randomization

Evidence from non-randomized data from RCTs

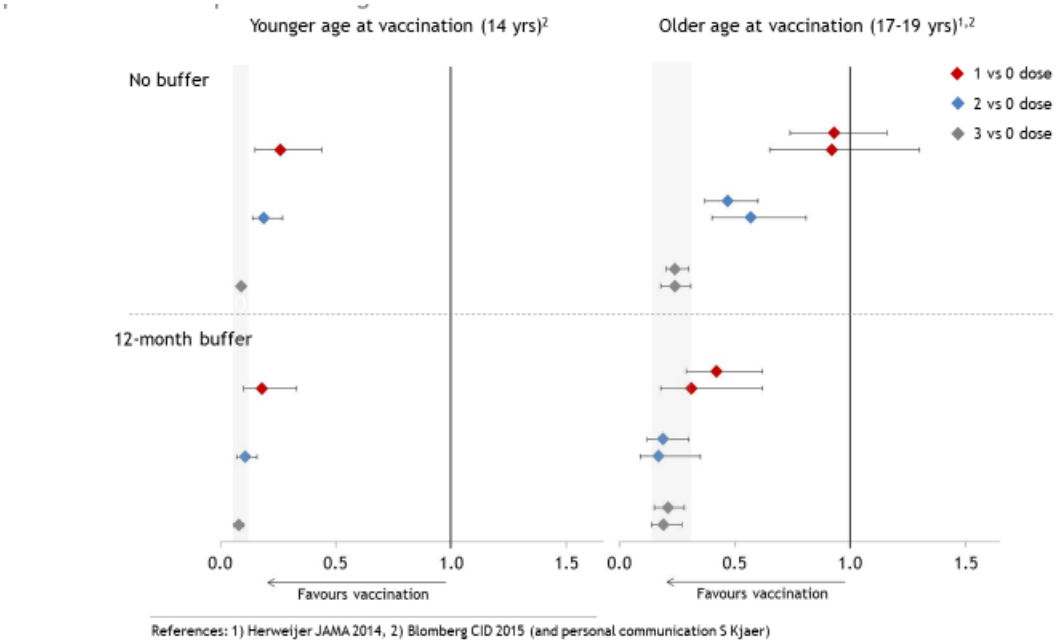
Observational data from both the Costa Rica Vaccine Trial and the India trial suggested similar vaccine effectiveness with one, two and three doses. While GMTs are lower after one dose, the durability of the antibody responses were similar after one and three doses. The clinical relevance of GMTs however is unknown, as to date there is no known titre which that can be used as a correlate of protection from infection and/or disease.

Evidence from observational studies

For the post-licensure observational studies, similar to the systematic review by the Cochrane Response, the Single-dose HPV Vaccine Evaluation Consortium found serious risk of bias in most studies. Most biases are likely to impact estimates towards lower effectiveness of one and two doses compared with three doses; due to females not completing three-dose recommended schedule being often older at time of vaccination, from lower social economic status, and having indicators of higher risk.

While most studies showed greater effectiveness with three doses followed by two doses and one dose, studies, that stratified by age at vaccination, or were limited to persons vaccinated at a younger age, found less difference by dose. The reviewers attempted to address known biases by using buffer periods to exclude outcomes caused by prevalent infections at the first dose and by stratifying the results by age at vaccination. In examples given, differences in effectiveness by number of doses decreased or were eliminated when using longer buffer periods or restricting analyses to girls vaccinated at younger ages. There was no direct comparison of two doses vs one dose of HPV vaccine.

Figure 7 Effectiveness against anogenital warts by number of doses – impact of buffer period and age at vaccination



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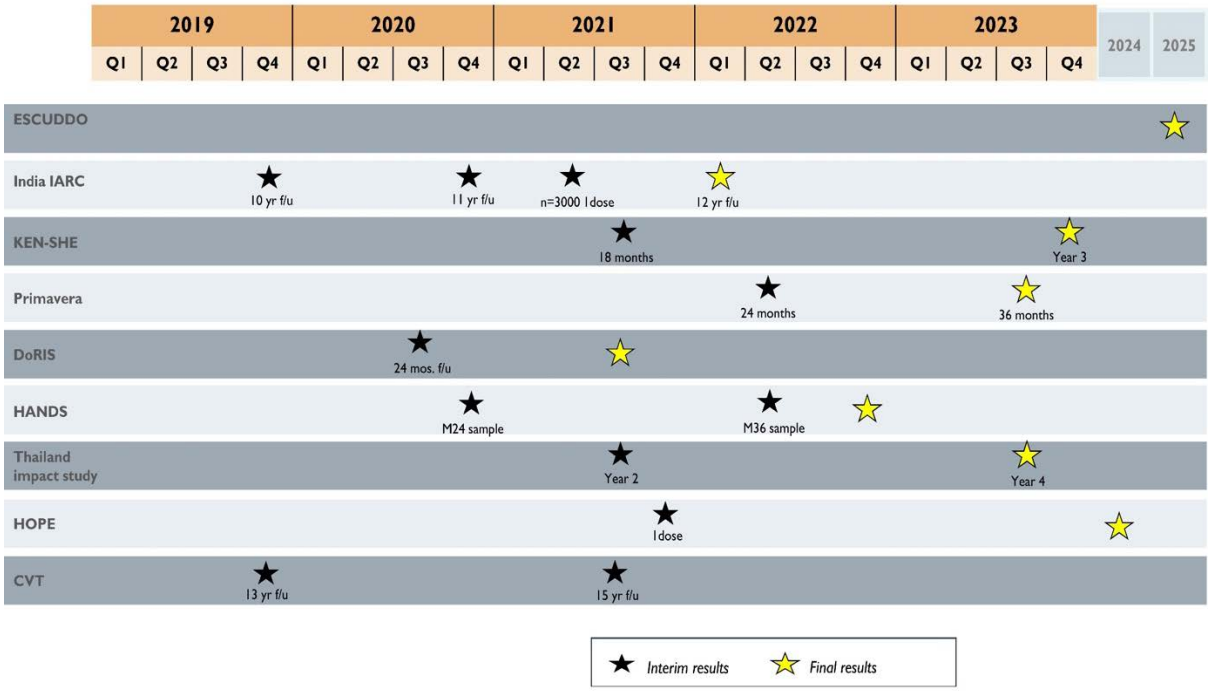
Clinical trials ongoing or planned to further assess 1 dose schedules

A number of clinical trials are ongoing to assess the effect of single-dose schedule and extended interval between doses. Table 2 below provides an overview of the timelines for various initiated, prospectively designed studies intended to formally evaluate single dose protection from HPV vaccines.

Table 2. Timeline of ongoing single-dose HPV vaccine and on efficacy and immunogenicity research from randomized controlled trials and community impact studies



HPV vaccination schedules - Different intervals between the first and second doses

The Working Group also reviewed a Cochrane Systematic Review[12] on the assessment of evidence of longer interval versus shorter interval between two HPV vaccine doses. The systematic review included data from two RCTs comparing longer interval (6 or 12 months) between doses of bivalent HPV vaccine in females aged 9 to 14 years; one cluster RCT comparing four different interval schedules between doses of bivalent HPV vaccine, one RCT comparing 12 months with 6 months interval between doses of nonavalent HPV vaccine in females and males aged 9 to 14 years; two post-hoc analysis of RCTs: one comparing a 6-month interval with a 1-month interval of bivalent HPV vaccine in females aged 18-26 years and the other comparing a 6-month interval with a 2-month interval of quadrivalent HPV vaccine in females aged 10-18 years; one observational cohort study comparing a longer (>90 days) with a shorter interval (<90 days) of bivalent vaccine in females aged 10-11 years and eleven observational cohort studies which compared longer intervals with shorter intervals of quadrivalent HPV vaccines. The durations of intervals being compared in each study are listed in table 3.

The risk of bias for all studies and outcomes was assessed and varied depending on the outcome being assessed.

Evidence from randomized studies (see pages 4-16 of the systematic review report)

For bivalent HPV vaccine, evidence from one study (Canada/Germany1) showed higher GMTs for HPV 16/18 at one month follow up after the last dose and at 24 months in females aged 9 to 14 years receiving the vaccine with a 6-month interval between doses compared with 2-month interval (moderate certainty evidence). Another study (Multinational2) showed higher GMTs for HPV 16/18 at one month after the last dose and 36 months after the first dose in females aged 9 to 14 years receiving the vaccine with a 12-month interval between doses compared with a 6-month interval (high certainty evidence).

However, the same study (high certainty evidence) showed no difference on seroconversion to HPV 16/18 between 12-month and 6-month intervals at 1 month after the last dose.

For quadrivalent HPV vaccine, evidence from one study (Vietnam 1) showed that there were little to no difference on GMTs for HPV 16/18 at 6 months following the second dose in females aged 11 to 13 years receiving the vaccine with a 6-month interval between doses compared with a 3-month interval (moderate certainty evidence).

[12] 'Longer interval versus shorter interval between two HPV vaccine doses' presented by Cochrane Response on the SAGE Working Group on HPV immunization meeting on 6-7 June 2019.

One study (Multinational3) showed higher GMTs for all HPV genotypes except for HPV 45, in those receiving nonavalent HPV vaccine with a 12-month interval between doses compared with a 6-month interval (high certainty evidence). The study also showed no difference on seroconversion to all HPV types between groups at one month after the last dose (high certainty evidence).

Post-hoc analyses of RCTs (see pages 17-28 of the systematic review report)

The two post-hoc analysis of RCTs (Costa Rica1 and India1, low certainty evidence) revealed that there were higher GMTs following a longer interval (6 months) than a shorter interval (1 or 2 months) between two doses of bivalent HPV vaccine up to 84 months, or quadrivalent HPV vaccine up to 36 months.

Due to imprecision and limitations in study design, there was mostly very low certainty evidence on clinical outcomes (incident and persistent HPV infection) from these two studies when a longer interval schedule was compared with a shorter interval schedule.

Observational cohort studies (see pages 29-30 of the systematic review report)

Data from observation cohort studies was considered to be at serious risk of bias, except for one study which had moderate risk of bias (USA2). The interval comparisons made by these studies varied and so could not be included in the meta-analysis.

From the results of four observational studies (Fiji1, USA7, USA8, Australia1), there were either no difference or better immunogenicity and histology outcomes following a longer interval schedule compared with a shorter interval (more than 6 months interval versus less than 6 months interval) between doses.

The clinical relevance of GMTs however is unknown, as to date there is no known titre as a correlate of protection form infection and/or disease.

Five studies reported on the incidence of genital warts (Denmark2, Sweden2, USA2, USA6, USA11) comparing different intervals between two doses of quadrivalent HPV vaccine. From these studies, two reported estimated in favor of longer intervals between doses, two reported no difference, and one reported an estimate in favor of a shorter interval. The intervals compared in the different studies were too heterogeneous to allow meta-analyses. Denmark2 compared a two-month interval to intervals of 3, 4, 5, and 6 months. Sweden2 compared an 8+ month interval between doses with a 4-7-month interval or a 0-3-month interval. USA2 compared a $\geqslant$6 months interval with a <6 months interval. USA6 compared a 5 or more months, with <5 months between doses. USA11 compared a $\geqslant$6-month interval with < 6-month interval. The study at lowest risk of bias (USA2) reported an estimate in favor of a longer interval.

Table 3. Studies included in systematic review on different schedule intervals

Study	Design	Vaccine	Comparison (months)	Number of participants	Outcomes
Canada/Germany1	RCT	Bivalent	6 vs 2	241 vs 240	GMT, seroconversion
Multinational 2	RCT	Bivalent	12 vs 6	415 vs 550	GMT, seroconversion
Vietnam1	Cluster RCT	Quadrivalent	6 vs 3	193 vs 197	GMT
Multinational 3	RCT	Nonavalent	12 vs 6	301 vs 602	GMT, seroconversion
Costa Rica1	Post-hoc analysis of RCT	Bivalent	6 vs 1	52 vs 140	GMT, HPV incidence
India1	Post-hoc analysis of RCT	Quadrivalent	6 vs 2	4,979 vs 3,452	GMT, HPV incidence
Australia1	Retrospective cohort	Quadrivalent	>6 vs <6	7,204 vs 20,297	histological (any high grade, CIN3/AIS, CIN2)
Denmark2	Retrospective cohort	Quadrivalent	3, 4, 5, 6 vs 2	Interval n values: NR 2 dose: 93,519	anogenital warts
Denmark/Sweden1	Retrospective cohort	Quadrivalent	≥5 vs 4	44,021 vs 513,507	CIN2+
Fiji1	Prospective cohort	Quadrivalent	≥6 vs <6	Interval n values: NR 2 dose: 60	GMT
Sweden2	Retrospective cohort	Quadrivalent	≥8 vs 4-7 vs 3	1,894 vs 8,095 vs 204,103	anogenital warts
Uganda1	Prospective cohort	Bivalent	>3 vs ≤3	28 vs 113	GMT
USA1	Retrospective cohort	Quadrivalent	≥6 vs <6	228 vs 376	abnormal cervical cytology
USA2	Retrospective cohort	Quadrivalent	≥6 vs <6	2,729 vs 2,730	anogenital warts
USA6	Retrospective cohort	Quadrivalent	≥5 vs <5	17,826 vs 18,757	anogenital warts
USA7	Retrospective cohort	Quadrivalent	>3 vs <3	126 vs 39	GMT
USA8	Retrospective cohort	Quadrivalent	≥8 vs 51-70 days	198 vs 192	GMT
USA11	Retrospective cohort	Quadrivalent	≥6 vs <6	16,990 vs 21,552	anogenital warts

HPV vaccination schedules - Number of doses in older age group

The Working Group also reviewed a Cochrane Systematic Review[13] on the assessment of effectiveness of two doses of HPV vaccine in females and males who received their first doses aged 15 to 18 years, compared with no vaccine or three doses of HPV vaccine. The systematic review included 6 studies: (i) one RCT conducted in Canada and Germany, one post-hoc observational analysis of a RCT in India, and three retrospective cohort studies conducted in Denmark and the USA, which reported results on bivalent and quadrivalent HPV vaccines in females and (ii) one retrospective cohort study conducted in USA (USA11) which reported unstratified results in females and males on quadrivalent HPV vaccines.

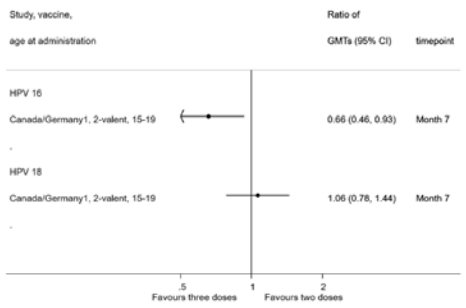
No evidence exclusively on males or on the nonavalent vaccine were identified for two doses of HPV vaccine in this specific age group.

Evidence from randomized data

A study (Canada/Germany1, moderate certainty), showed evidence that at one month after the last dose, two doses of bivalent HPV vaccine were non-inferior to three doses in females aged 15 to 19 years for GMTs of HPV 18, but non-inferiority was inconclusive for GMTs of HPV 16. (see pages 9-10 from the systematic review)

Figure 8: Two doses versus three doses bivalent HPV vaccine in 15-19 year-old-females – immunogencitiy outcomes

Participants: 15 to 19-year old females (seronegative at baseline)
Setting: Canada and Germany
Comparison: Two doses bivalent HPV vaccine (month 0, 6) versus three doses (month 0, 1, 6) bivalent HPV vaccine

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs for HPV 16 and 18 Follow up: 7 months (Canada/Germany1)		⊕⊕⊕O MODERATE

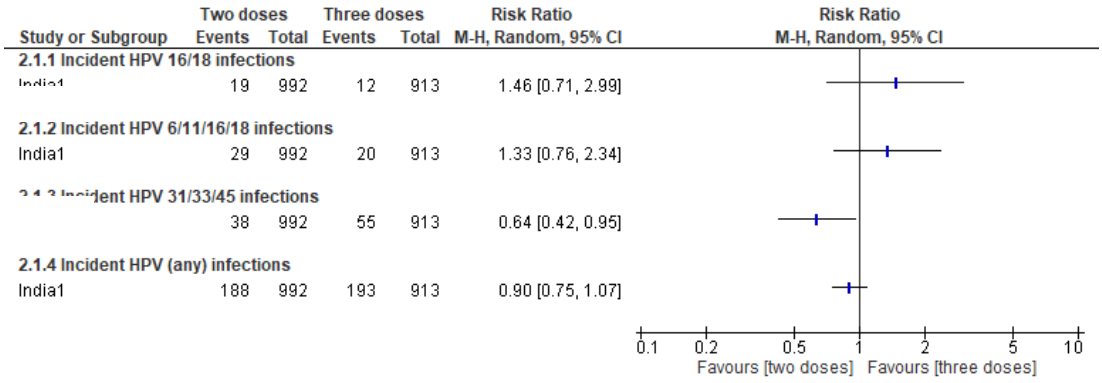
CI= confidence interval; HPV= human papilloma virus; GMT= geometric mean titre

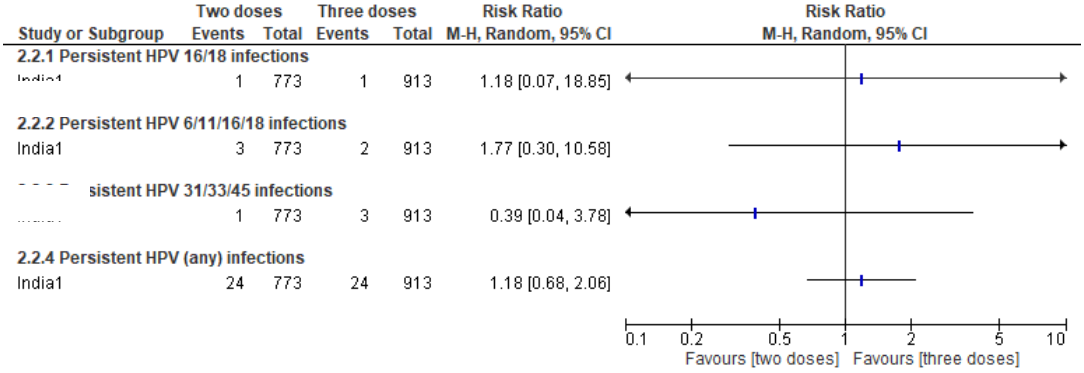
Post-hoc analyses of RCTs

A post-hoc analyses of one RCT (India1, very low certainty evidence) was inconclusive on incidence of CIN1, CIN2, CIN3, persistent and incident HPV infection when comparing two doses with three doses of the quadrivalent vaccine in 15 to 18-year-old females.

[13] 'Two doses HPV vaccine compared with placebo, no vaccine, or three doses in females and males who received their first dose aged 15 to 18 years' presented by Cochrane Response on the SAGE Working Group on HPV immunization meeting on 6-7 June 2019.

Figure 9: HPV infections in post-hoc analysis of India trial comparing two doses with three doses of quadrivalent HPV vaccine in 15-18-year-old.





Evidence from observational studies

Two doses compared to no vaccination

For the quadrivalent HPV vaccine one study in India (India1, low certainty evidence) showed that compared to no HPV vaccination, in females aged 15 to 18 years at the time of the first dose, two doses resulted in fewer cases of incident HPV infections; very low certainty and inconclusive evidence on persistent HPV infections; and two doses compared to no HPV vaccination reduced abnormal cervical cytology (very low certainty evidence). (see pages 4-8 of the systematic review)

From a study in USA (USA1) females vaccinated at a younger age (15 to 16 years) showed a stronger response in terms of reduced abnormal cervical cytology than females vaccinated at an older age (17 to 18 years). In females aged 15 to 17 years

at the time of the first dose, two doses reduced the incidence of anogenital warts compared with no vaccine (very low certainty evidence; see page 8 of the systematic review report).

Two doses compared to three doses

In addition, in females aged 15 to 18 years when receiving the first dose, two doses of quadrivalent vaccine were non-inferior to three doses for GMTs of HPV 6/11/16/18 measured at 7 months (low certainty evidence), and that non-inferiority was maintained up to 48 months for these outcomes (see pages 11-13 of the systematic review); and the effects on incidence of CIN grade 1 to 3, abnormal cervical cytology, and persistent and incident HPV infections were inconclusive (India1,very low-certainty evidence).

One study (Denmark2) found that the rate of anogenital warts in females aged 16-17 at the time of the first quadrivalent HPV vaccine dose was higher after two doses compared with three doses up to 6 years of follow up (low certainty evidence). Another study (USA11) found little or no difference between two and three doses on the incidence of anogenital warts in females and males aged 15-19 years at 3 months to 5 years follow-up (very low certainty evidence). Results from these two studies were not pooled due to methodological heterogeneity.

Global supply and demand balance of HPV vaccines

WHO Market Study

The Working Group reviewed the WHO Market Information for Access to Vaccines (MI4A) study ran in early 2019 to estimate the available supply for commercialization, to understand size and shape of global vaccine demand, and to estimate global supply and demand balance and access risks/opportunities. MI4A applies a standardized methodology reviewed and endorsed by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC).

Available supply for commercialization (ASC) – the number of doses available for sale at global level in one typical year with normal production facilities utilization across the various vaccines (not factoring in special market, regulatory or technical events) was estimated based on data collected from manufacturers, review of clinical trials data, review of product documentation from the US FDA and European Medicines Agency, literature review, validation with BMGF, CHAI, Gavi, and PATH and triangulation with demand data. Three products are currently available on the market and four are in advanced clinical development. It is estimated that supply will grow slowly in the short term, followed by a steep ramp up in 4-6 years. Three supply scenarios were developed (high, base and low) to account for uncertainty around key drivers and define a supply range.

Seven demand scenarios were analyzed with input and consultations of WHO regional offices, BMGF, CDC, CHAI, Gavi, PATH, PAHO Revolving Fund, PATH (Table 4). The general assumptions in the seven scenarios includes: all countries introduce HPV vaccine by 2030; and gender-neutral vaccination only in countries with existing national recommendations. For scenario 1 (base case) the results forecasted a demand that reaches 120 million doses in 2025 and stabilizes at 130 million doses after that. Due to supply constraints in recent years, multiple age cohort (MACs) have been distributed across years but remain an important contributor to required supply in the next 5 years.

The single-dose demand scenarios assumed that all lower-income countries (LICs) and MICs that have already introduced and future introductions switch to single-dose schedule in 2022. High-income countries remain at two doses. They also assumed 1.15 times higher coverage up to 90% for countries. In these scenarios, required supply is considerably lower from 2022 as expected and the demand plateaus at 80 million doses by mid 20s.

For the 3-year extended interval demand scenario, it was assumed that all Gavi-supported countries, PAHO Revolving Fund countries and Mexico would adopt a 3-year extended interval schedule from 2020 or future introduction year. This applied to countries already introduced and future HPV vaccine introductions. The coverage of the first dose was assumed at 1.15 times higher and up to 90% for the first dose, while the second dose was assumed at 0.7 times the base coverage. No MACs were implemented. Given assumptions of early application of this schedule, results

revealed that the demand in this case is lower than all other scenarios for 2020-21 while nearly reaching the base-case scenarios (Scenario 1) from 2025.

Table 4. Demand scenarios of MI4A study

Demand Scenarios	Description
S1: Routine 2 doses with MACs 9-14 years old *	Routine: 2 doses MACs: 2 doses
S2: Routine 9 years old, 2 -doses (No MACs) *	Routine: 2 doses
S3: Routine 1 dose with MACs 9-14	Routine: 1 dose for LICs & MICs from 2022 MACs: 1 dose for LICs & MICs from 2022
S4: Routine 1 dose (No MACs)	Routine: 1 dose for LICs & MICs after 2022
S5: 3-year extended interval	Routine: 1+1 dose (3-year interval) for Gavi-supported and PAHO Revolving Fund countries (plus Mexico) from 2020 or intro year
S6: 5-year extended interval + 14-year-old girls catch-up	Routine: 1+1 dose (5-year interval) for Gavi-supported and PAHO Revolving Fund countries (plus Mexico) from 2020 or intro year Catch-up: 2 doses (14- year-old girls) for 5 years for all introducing countries implementing 1+1 schedule
S7: 14-year-old, later switch to 9-year-old	Routine: 2 doses at 14 years old to start, adding 9-year-old when supply available (2 doses for 14yo continue for five years after 9yo added) for new introductions in Gavi, PAHO RF and LMICs

MACs, multiple age-cohorts vaccination; LICs, lower-income countries; MICs, middle-income countries

* Forecasting China will introduce sub-nationally with 3 doses then change to 2 doses in 2024

The 5-year extended interval and catch-up scenario assumed all Gavi-supported countries, PAHO Revolving Fund countries and Mexico would adopt a 5-year extended interval schedule from 2020 or future introduction year. This applied to countries that have already introduced and future HPV vaccine introductions. In the interim years of the extended interval, the 14-year-old cohort receives catch-up vaccinations with two doses. The coverage of the first dose was assumed at 1.15 times higher and up to 90% for the first dose, while the second dose was assumed at 0.7 times the base coverage. Given catch up dose requirements, this scenario resulted in

lower demand than the base-case scenario (Scenario 1 and Scenario 2) for 2020 to 2024, but higher than scenario 5 (3-year interval).

Scenario 7 assumes all future introductions in Gavi, PAHO and lower middle-income countries (LMICs) start with a target of 14 years old girls, with a later switch to 9 years old when sufficient supply is available (once 9-year-old is added, 2 doses at 14 years continues for 5 years). Gavi countries that have recently introduced HPV vaccine but have not caught up all girls up to 14 years are assumed to include 2 doses for 14-year-old for the required number of years (1-4). High income and Upper MICs remain as per the base case. This scenario resulted in lower demand than the base-case scenario (Scenario 1) for 2020 to 2024, but higher than scenario 5 (3-year interval). Annual demand was similar, but slightly higher, than scenario 6 (5-year interval + catch-up).

Leveraging supply and demand estimates, a dynamic supply and demand balance analysis was conducted. For each year when supply was not sufficient to cover estimated demand, available supply was allocated to countries reflecting an understanding of current market dynamics. A minimum 10% and a desired 30% of extra supply have been applied to define balance and risk based on considerations of demand and supply characteristics (e.g. introduction status and demand visibility, supply concentration and dependences from other production processes)

Results showed that in the short-term, supply remains constrained or at high risk especially for LICs and LMICs across all scenarios. Scenarios with no MACs allow minimization of impact of supply constraint. The balance is expected to improve in the mid-term subject to manufacturers' success in expanding their capacity; pipeline producers' success in reaching markets and obtaining pre-qualification; and countries' acceptance of all products irrespective of valency or country of origin. If conditions are not verified, only one dose scenario would relieve shortages and risk in mid and long term.

Impact of different HPV immunization strategies in the context of supply constraint

HPV-ADVISE (Agent-based Dynamic model for Vaccination & Screening Evaluation)[14]

The Working Group was presented with a mathematical modeling analysis estimating optimal distribution of vaccine by year and country that would prevent the greatest number of cervical cancer cases over 100 years, in the context of supply constraint.

Optimal vaccination strategies were defined in terms of vaccination efficiency (i.e. minimize the number needed to vaccinate [NNV] to prevent one cervical cancer

[14] Brisson M, Laprise JF, Chesson HW, Drolet M, Malagon T, Boily MC, et al. Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. J Natl Cancer Inst 2015 Oct;108(1).

case), return on investment (i.e. identify the most cost-effective strategy by incremental cost-effectiveness ratio [ICER]), and optimal vaccine distribution (i.e. maximize global cervical cancer cases prevented for vaccine doses available).

To assess the impact of HPV vaccination on burden of disease in the context of limited vaccine supply, the model examined four different vaccination strategies which varied with regard to age of routine vaccination (9 or 14 years old), sex of target population (females only or gender-neutral), vaccine schedules (current or extended 2-dose strategies), number of age-cohort vaccinated (catch-up or MACs), and number of doses used (1 or 2 doses).

All strategies targeting females aged 9 to 14 years, with or without MACs, produce low NNV and ICERs, suggesting that vaccinating this group would be efficient and cost-effective.

The optimal (most efficient and cost-effective) strategy was routine vaccination in females aged 9 years with 5-year extended interval between the first and second doses together with catch-up vaccination in females aged 14 years in the first 5 years.

Gender-neutral vaccination would lead to an additional reduction in cervical cancer incidence due to herd protection. However, such a strategy would double the vaccine doses required and lead to diminishing returns compared with girls-only vaccination.

Single-dose vaccination schedule was also explored by modeling lower vaccine efficacy and duration of protection. This analysis showed that the impact on cervical cancer incidence of differences in duration of vaccine protection is larger than that by vaccine efficacy.

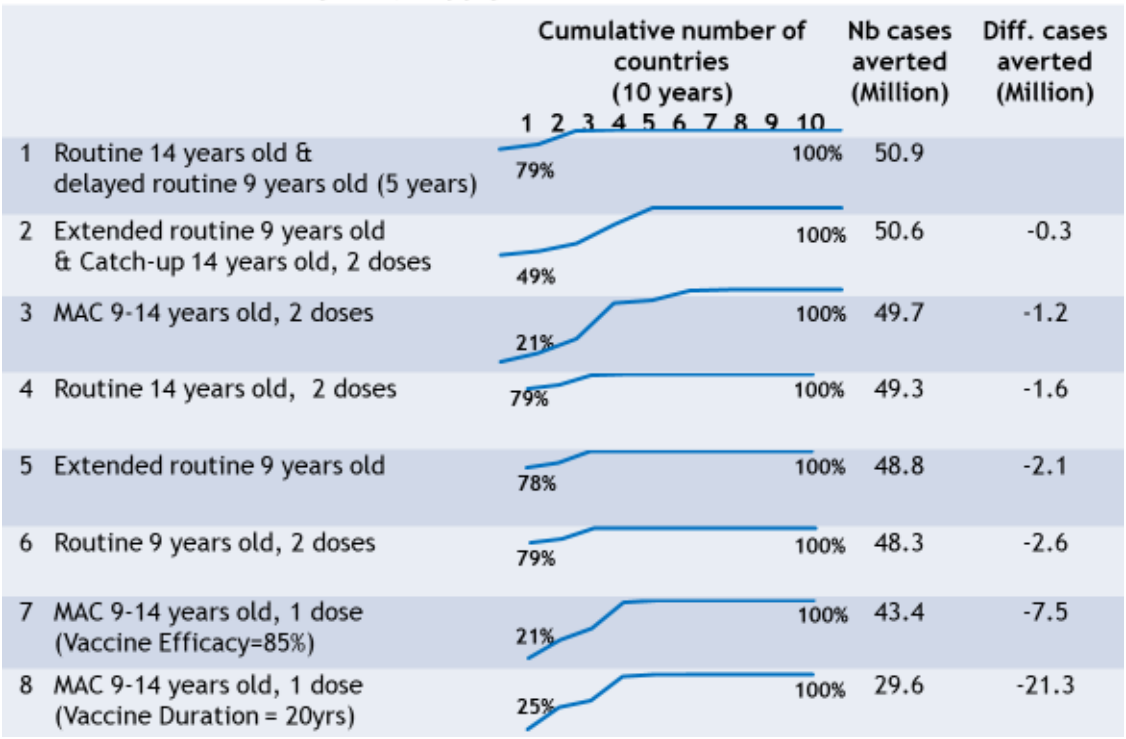
For 92 LMICs which have yet to introduce HPV vaccine, the model estimated the optimal distribution of vaccine by year and country that would prevent the greatest number of cervical cancer cases over 100 years.

The strategies that optimized cervical cancer prevention under supply constraint were: (1) routine vaccination in one cohort of females aged 9 years with 5-year extended interval between the first and second doses together with catch-up vaccination in a second cohort of females aged 14 years in the first 5 years; and (2) routine vaccination of only one cohort of girls (i.e. those aged 14 years) for 10 years together with delayed routine vaccination of a second cohort of younger girls (i.e. aged 9 years) for 5 years.

The first strategy was estimated to be most efficient (lowest number needed to vaccinate, NNV), to be most cost-effective and to maximize cervical cancer reductions followed by the second strategy.

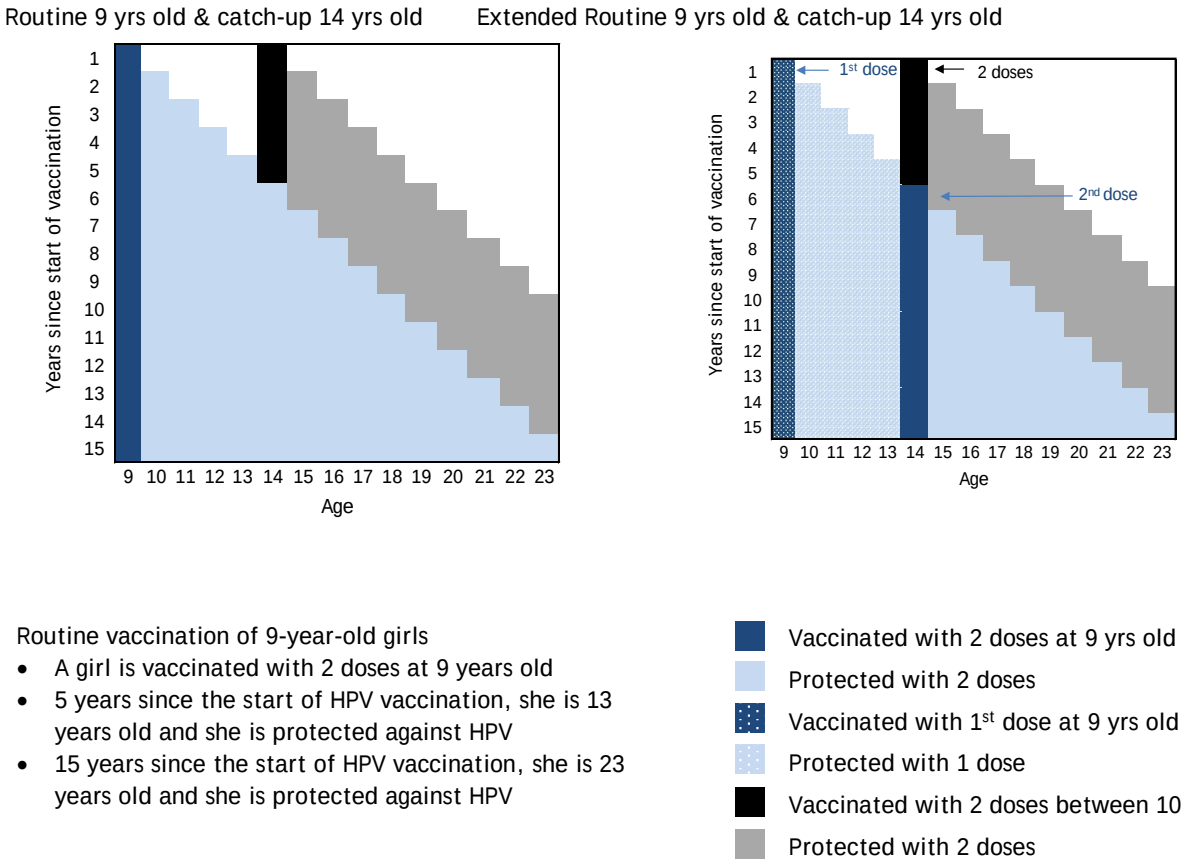
Once evidence on single-dose schedule is deemed sufficient for a policy recommendation, switching to a single-dose strategy, would accelerate the benefits.

Figure 10. Comparison of cervical cancers cases prevented among different vaccine schedule scenarios (HPV-ADVISE model)



Two strategies were therefore predicted to be optimal within and between countries using the population perspective. These strategies maintain the recommended two-dose schedule and minimize the impact of delay due to vaccine supply constraint, while facilitating the switch to single-dose once evidence is deemed sufficient.

Figure 11. Optimal vaccination strategies by HPV-ADVISE model



PRIME (Papillomavirus Rapid Interface for Modelling and Economics)[15]

The Working Group reviewed a mathematical modeling analysis estimating the impact of different MI4A supply and demand scenarios on burden of disease taking market forces into consideration. This modeling exercise assumed as did the MI4A study above, that in case of supply constraints, higher income and upper middle-income countries would be served first, pool procuring countries second and Gavi supported countries and other middle-income countries last.

Several scenarios were examined about vaccine distribution, including (i) distributing vaccines according to MI4A supply projections, (ii) distributing vaccines according to cervical cancer incidence, (iii) using an optimization algorithm to distribute vaccines in order to maximize the number of cancers or deaths prevented within the supply constraints provided by MI4A.

Similar to the HPV-ADVISE results, the scenarios that include MACs predicted the greatest number of cervical cancer cases averted, while scenarios without MACs miss

[15] Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health 2014; 2: e406–14.

certain age-cohorts and as such avert fewer cases of cervical cancer. This was true whichever scenario about vaccine distribution was applied.

However, not implementing MACs reduces current vaccine demand. An extended interval between the first and second doses would help minimize current vaccine supply requirements.

The strategy that optimized cervical cancer prevention under supply constraints was routine vaccination in one cohort of females aged 9 years with 5-year extended interval between the first and second doses together with catch-up vaccination in a second cohort of females aged 14 years in the first 5 years (scenario 6 in Table 4).

This strategy assumes two-dose schedule per cohort and contributes to address issues to vaccine supply constraint compared with using MACs, while facilitating the switch to single-dose schedule once and if evidence is deemed sufficient.

CONCLUSIONS

On barriers to access to HPV vaccines

Ongoing challenges for HPV vaccine introduction include competing vaccine priorities, perception of burden of disease and risk of cervical cancer, affordability of HPV vaccines, especially in non-Gavi MICs, political commitment from relevant policy makers, knowledge and acceptability of HPV vaccines, and programmatic issues.

In addition, the supply of HPV vaccines is predicted to remain constrained for the next three to five years which will particularly jeopardize plans for new HPV vaccine introductions and MACs.

The Working Group is also aware that barriers to reaching high coverage of HPV vaccination after introduction include choice and sustainability of vaccine delivery strategies, vaccine acceptance and hesitancy, equity in accessibility of the vaccine, and access barriers in insurance-based reimbursement systems.

The Working Group reiterates that all countries should introduce HPV vaccine and maintain a high coverage to prevent HPV infection and cervical cancer. The Working Group concludes that monitoring the global demand and supply of HPV vaccines would contribute to create and maintain a healthy market.

On HPV vaccination schedules

For the prevention of cervical cancer, the Working Group concludes that the current WHO recommendation on HPV vaccination (targeting females aged 9 to 14 years with 2 doses of HPV vaccine) remains valid.

There is emerging evidence from observational studies that suggests that a single-dose HPV vaccination schedule may be effective, however the evidence is not sufficient to support a change in the current WHO recommendation.

Emerging evidence from observational studies needs to be interpreted with caution as observational studies are susceptible to bias and confounding. The majority of studies reviewed were deemed to be affected by moderate to serious risk of bias. Data suggests that one dose of HPV vaccine provides certain protection compared with no vaccine, but results are inconclusive when compared with two or three doses.

The Working Group acknowledges the advantages of a single-dose schedule. Randomized evidence from ongoing clinical trials on single-dose schedule is expected to be available starting mid-2021. These will provide additional evidence on the efficacy of one dose of HPV vaccine.

A longer interval between two doses of HPV vaccine appears to result in higher GMTs (also non-inferior) compared with a shorter interval between doses. There is evidence from other vaccines that longer intervals between doses gives enhanced antibody responses. Infection risk in females 9 to 14 years of age may be lower than in those 15 to 19 years of age. Completing full course of vaccine before becoming sexually active would lower the risk of infection.

The Working Group also concludes that the non-inferiority of two doses of HPV vaccines compared with three doses in females aged 15 to 18 years when receiving the first dose is inconclusive. The evidence was of very low certainty, often due to low numbers of events and risk of bias due to confounding in observational studies.

On HPV vaccine global supply and demand

Based on the scenarios reviewed, in the short-term, HPV vaccine supply remains constrained or at high risk especially for LICs and LMICs across all scenarios.

It is estimated that the scenarios of two-dose (6 months or 3 years intervals) or single-dose with no MACs (scenarios 2, 4, and 5 in Table 4) may minimize the impact of supply constraint, with only 2 countries' introductions being estimated to delay in 2021, despite very tight supply demand balance requiring careful management. However, in this case, without any catch-up, some girls would miss the vaccination opportunity.

All scenarios that include MACS or catch-ups, even a 5-year extended interval, do not fully alleviate short-term supply constraints, delaying introductions/catch ups over the course of the next 3 years (scenarios 1, 3, and 6 – with scenario 6 performing relatively better).Vaccinating multiple age-cohorts with two-dose schedule (scenario 1) would delay planned introductions in several countries (including high burden countries) until 2023. Single-dose schedule with MACs (scenario 3) would ease supply constraints earlier, but planned introductions in some countries (including high burden countries) may be to delay until 2022.

Fewer countries (including high burden countries) are predicted to delay planned introductions in 2020 and 2021 in scenario 6 (routine vaccination in females aged 9 years with 5-year extended interval between the first and second doses together with catch-up vaccination in females aged 14 years in the first 5 years).

The two scenarios with extended interval between the first and second doses also help accelerate introductions with very careful management of supply and demand.

The supply and demand balance are expected to improve in the mid-term subject to current vaccine suppliers' success in expanding their capacity; pipeline producers' success in reaching the markets and pre-qualification; and country acceptance for all products irrespective of valency or country of origin.

On efficiency and cost-effectiveness of different HPV immunization strategies

The HPV immunization strategy of routine vaccination in females aged 9 years with 5-year with extended interval between the first and second doses together with catch-up vaccination in females aged 14 years in the first 5 years, is predicted to be the most efficient and cost-effective strategy

All strategies targeting girls between 9 and 14 years old, with or without multiple age cohorts (MAC), produce low NNV and incremental cost-effectiveness ratios. They are highly efficient and cost-effective.

Vaccinating boys & older women were much less efficient and cost-effective versus vaccinating girls between 9 and 14 years old but remained below the GNI per capita cost-effectiveness threshold.

Optimal strategy in the context of limited vaccine supply

Under vaccine supply constraint based on the two models (HPV-ADVISE and PRIME), using different assumptions the strategies that optimized cervical cancer prevention under supply constraints were: (i) routine 2 doses 14 years old and later switch to routine 9 years old and; (ii) routine 2 doses 9 years old with 5-year extended interval; 14-year-old catch-up.

The conclusions were robust to variations in supply constraints. Same strategies were estimated to maximize cervical cancer reductions.

Switching to 1 dose schedule once the evidence is deemed sufficient (e.g., vaccine efficacy is comparable to 2 doses) could accelerate benefits and contribute to alleviate supply constraints & accelerate introduction in countries

It requires the least number of vaccines to prevent one cervical cancer case (the most efficient) and the lowest incremental cost per disability-adjusted lie year (the most cost-effective) at both country and global levels.

This strategy is predicted to be optimal within and between countries using the population perspective and would lead to the greatest number of cervical cancer cases prevented in the context of global supply constraint of HPV vaccine. It maintains a two-dose schedule and minimize the impact of delay of introduction due to vaccine supply constraint, while facilitating the switch to single-dose schedule once evidence is deemed sufficient. The group acknowledged that programmatic challenges in reaching girls after 5 years for the second dose need to be carefully considered and strategies to address them implemented.

RECOMMENDATIONS

For the prevention of cervical cancer, the Working Group reaffirms the following WHO-recommendations for the use of HPV vaccines:

1. The primary target population for HPV vaccination should continue to be girls aged 9-14 years, prior to becoming sexually active, with a two-dose schedule[16]. If pertinent, a 3-dose schedule (0, 1–2, 6 months) should be used for all vaccinations initiated ≥15 years of age, including in those younger than 15 years known to be immunocompromised and/or human immunodeficiency virus (HIV)-infected (regardless of whether they are receiving antiretroviral therapy).

   However, vaccination of secondary target populations, for example, females older than 14 years or males of any age, is recommended only if this is feasible, affordable, cost-effective, and does not divert resources, including depleting global vaccine supply from vaccination of the primary target population.

   HPV vaccines should be introduced as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. This strategy should include education about reducing behaviors that increase the risk of acquiring HPV infection, obtaining the support of leading health professionals, training of health workers and information to women about screening, diagnosis and treatment of precancerous lesions and cancer. The strategy should also include increased access to quality screening and treatment services and to treatment of invasive cancers and palliative care.

2. The Working Group reiterates that all three licensed HPV vaccines have excellent safety, efficacy, immunogenicity and effectiveness profiles. All countries should introduce HPV vaccine and maintain a high coverage to prevent HPV infection and cervical cancer. Current evidence suggests that from the public health perspective the three licensed HPV vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer, which is mainly caused by HPV types 16 and 18.

Concerned by the global situation of constrained HPV vaccine supply, the Working Group proposes the following additional recommendations:

3. The Working Group underlines the importance of fair global distribution of HPV vaccines and flexibility of vaccination strategies. Therefore, the Working Group encourages SAGE to make a strong statement about the need for a more equitable global allocation of limited HPV vaccine supply across countries based

[16] World Health Organization. Human papillomavirus vaccines: WHO postion paper, May 2017. Weekly epidemiological record 2017;19(92):241-68. https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf

on public health considerations and requests WHO to take a more active role in facilitating such allocation.

4. The Working Group requests SAGE to encourage manufacturers to expand the number of vaccine doses that are available to females in low- and middle-income countries as they include the settings where the burden of cervical cancer is the greatest so as to increase the vaccination coverage in females from these settings.

5. Introduction of MACs, gender-neutral and older age group vaccination strategies in any countries should be temporarily postponed until all countries have been able to introduce HPV vaccination in at least one age-cohort (i.e. in at least one single-year age cohort) of the WHO recommended primary target which is girls, in the context of supply constraint. Although vaccine supply will remain limited, deferral of these strategies will significantly relieve constraints and prioritize the allocation of 2-doses to countries with a large burden of disease and per their introduction plans.

6. Countries introducing HPV vaccine should consider initially targeting one older cohort of girls (e.g. 13 or 14 years old) as this strategy will retain the maximum disease impact of HPV vaccination. These older girls may be closest to initiating sexual activity and at highest risk of exposure, therefore the protective benefit is greatest if they have a chance to be fully vaccinated. The programmatic challenges of reaching older girls and achieving high two-dose coverage must be carefully considered. If a significant number of girls initiate sexual activity before this age, the target cohort for immunisation can be altered accordingly. Once the global vaccine supply situation has improved (and by which time, sufficient evidence on a 1-dose schedule may be available) countries could consider then the following strategy options: (i) Continue with above strategy of targeting 13 or 14 year olds girls if high coverage is successfully being attained and, there is no problem with drop-out rates; (ii) Shift to a strategy of targeting younger 9 or 10 year old girls thus addressing any potential programmatic issues, drop-out rates, early sexual activity, and higher coverage. To accomplish this transition, countries can conduct one-time MAC vaccination for any cohorts not yet covered. Alternatively, for a time limited period, countries can combine targeting one younger cohort of girls (e.g. 9 or 10 years old) and one older age cohort (e.g. 13 or 14 years old) until all cohorts have been vaccinated.

7. Countries that have already introduced HPV vaccine and face an imminent vaccine supply shortage, a “1+1” schedule with an extended interval of 3-5 years for younger girls can be considered if an “off-label” recommendation is made. Use of this strategy presupposes that resources and commitment to reach the girls with the second dose exist. Finding these girls after an extended period of time may be challenging (potential high drop-out rate). The risks and benefits of “1+1” schedule targeting younger girls (e.g. 9 or 10 years old) is justified considering that 1 dose is better than zero dose; the antibody response is lower but the clinical

relevance of this is unknown, and risk of exposure during a longer interval period is assumed to be low in this young age group.

8. For countries that experience complete stock-outs of HPV vaccine, efforts should be made to ensure that eligible girls who were missed are vaccinated as soon as possible and before they turn 15 years old or before sexual activity commences if this is younger than 15 years old.

The Working Group welcomes the ongoing and planned trials assessing single-dose schedules and anticipate that they will be very useful to inform future policy recommendations. The Working Group also supports the ongoing population studies looking at population impact outcomes and at the impact of different numbers of doses received for both overall population and for populations with high background rates of HIV.

In vaccine effectiveness studies, the buffer period (that is, the lag time between vaccination and outcome counting) has been noted as an important factor to address any potential bias from prevalent infection. Allowance for buffer period substantially reduces the difference in the efficacy between one or two vaccine doses compared with three doses. This factor is more important for older females, and not younger age groups.

The Working Group recommends that the WHO Secretariat tracks new reports from an increasingly rich literature and considers additional analyses stratified according to risk of bias, and by age so as to provide further assessments of the effect a single-dose schedule compared with two-doses.

APPENDICES

Appendix I: Terms of Reference for the Working Group

Appendix II: List of participants (including Working Group membership)

Appendix III: Meeting agenda

Appendix I: Terms of Reference for the Working Group

Terms of Reference for the Strategic Advisory Group of Experts (SAGE) Working Group on potential contribution of HPV vaccines and immunization towards cervical cancer elimination

Background:

Despite the availability of effective prevention tools, cervical cancer continues to be a significant public health concern globally. Cervical cancer is the fourth most common cancer among women with 528,000 new cases and 266,000 deaths in 2012. Nearly 90% of these deaths were in low- and middle-income countries.

The WHO Director General plans to announce a global effort towards the elimination of cervical cancer at the World Health Assembly in May 2018. In preparation for this announcement, a WHO working group with the support of other UN agencies[17] and key partners is developing a full draft of the strategy document, including the definition of elimination and the main indicators and targets to reach the elimination goal. Following the WHA 2018 announcement, the strategy document, including the proposed definition and targets for elimination, will undergo stakeholder review and revision, with a global consultation anticipated in September 2018. A resolution on cervical cancer elimination will be considered at the Executive Board meeting in January 2019, and then put forward for endorsement and launch at the World Health Assembly meeting in May 2019. Moreover, HPV vaccine coverage was included in the WHO's Global Program of Work for 2018-2023, with the target of increasing vaccination coverage from 10% at baseline to 50% by 2023. This target is linked to the Sustainable Development Goals (3.7). There is also a Global STI Strategy target of 70% of countries having introduced HPV by 2020.

As of January 2018, 79 countries (41%) have introduced the HPV vaccine. At the current pace of introductions, the world is not on track to reach the 70% target by 2020. Most of the countries that have introduced the vaccine are high-income. So far, 94% of GAVI-eligible countries have not yet introduced the vaccine. It is anticipated that additional countries in Africa will introduce the HPV vaccine in the coming few years with GAVI support. Lower middle-income countries may continue to struggle to identify financing to support vaccine introduction. HPV vaccines are safe and highly effective but there are remaining issues related to affordability and challenges delivery. Recent changes in WHO recommendations have enabled countries to accelerate introductions, including opportunities for multi-cohort catch-ups. A recent vaccine supply shortage has limited the ability to meet country requests. Observational data suggest that a single-dose regimen could contribute to change this landscape of challenges by offering more flexible implementation

programs and reduced supply requirements. However, clinical trials assessing single-dose schedule are ongoing.

Terms of reference:

- To critically appraise the evidence and potential effect and cost effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination.
- To review the potential contribution of HPV vaccination towards cervical cancer elimination.
- To develop and propose interim goals that can be achieved through immunization as part of the efforts towards cancer elimination.
- To develop and propose indicators to monitor the accomplishment of these interim goals.
- To discuss and propose additional research related to vaccines and immunization needed to attain these goals and outline potential innovations that may help enhance the achievement of these goals.

Appendix II: List of participants (including Working Group membership)

World Health Organization

Expanded Programme on Immunization Plus
Initiative for Vaccine Research
Immunization, Vaccines & Biologicals

Meeting of the SAGE Working Group on Human Papillomavirus Immunization

Palace de Menthon, Menthod St-Bernard, France

6-7 June 2019

Final list of participants

SAGE members

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Shereen Bhutta, *Independent Expert, Professor and Head of the Department of Obstetrics and Gynaecology, Jinnah Postgraduate Medical Center, Karachi,* ***Pakistan (unable to participate)***

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Invited Experts

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Karene Yeung, Consultant, Implementation Research and Economic Analysis, Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Appendix III: Meeting agenda

Initiative for Vaccine Research (IVR)
Immunization, Vaccines and Biologicals (IVB)
World Health Organization

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MEETING OF THE SAGE WORKING GROUP ON HUMAN PAPILLOMAVIRUS IMMUNIZATION

6 – 7 JUNE 2019

Le Palace de Menthon
665 Route des bains
74290 Menthon St-Bernard, FRANCE

Agenda

Objectives

- To discuss preliminary outcomes of updated systematic reviews and meta-analyses on one-dose schedule and interval between doses of HPV vaccine, and all related evidence.
- To discuss vaccine allocation strategy(ies) to achieve more equitable access to HPV vaccines.
- To review the potential effect on HPV infection, disease and access to HPV vaccine in the short and mid-term of various schedule and vaccine allocation strategies

Expected output

- Evidence based recommendations for SAGE consideration on immunization schedules for HPV vaccines including assessment of the strength of evidence
- Evidence based recommendation on vaccine allocation strategies and their potential impact on access to vaccine, disease control and equity.
- Outline of evidence gaps and research needs to better inform this area of work.

Proposed questions to SAGE

Question 1: What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines (national policy, economic, acceptability, vaccine doses access other)?

Question 2: What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine and different intervals between the first and second doses of HPV vaccine? And what are the risks of bias of these studies?

Question 3: What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could the enhanced HPV vaccine supply allocation be?

Question 4: In light of the above conclusions/inputs, how should HPV vaccine introduction be prioritized with respect to impact and feasibility?

Day 1: Thursday 6 June 2019

Chair: Rakesh Aggarwal

OPEN SESSION

From 08:30	Registration	
09:00–09:30	Opening remarks Consultation objectives and tasks Introduction of participants Declaration of interests	WHO R. Aggarwal
Session 1: HPV vaccine uptake and barriers		
	Question 1: What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines (national policy, economic, acceptability, vaccine doses, access, other)?	
09:30–10:00	Update on HPV vaccine uptake and evidence related to main barriers	P. Bloem
10:00-10:30	Questions for clarification	Plenary
10:30–11:00	***Coffee***	
Session 2: Current evidence on HPV vaccine schedule		
	Question 2: What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine and different intervals between the first and second doses of HPV vaccine? And what are the risks of bias of these studies?	
11:00–11:30	Systematic review of evidence: • One-dose schedule of HPV vaccine • Different intervals between the first and second doses of HPV vaccines • Number of doses in the older group 15-18 years of age.	N. Henschke
11:30-12:00	Questions for clarification	Plenary
12:00–12:30	Single-Dose HPV Vaccine Evaluation Consortium Preliminary results regarding one dose	A. Kreimer
12:30-13:00	Questions for clarification	Plenary
13:00-14:00	***Lunch***	
Session 3: Inputs from industry on evidence and plans for supply (CONFIDENTIAL)		
14:00-15:00	Individual industry inputs (10' each) Questions (5')	Industry Reps

END OF OPEN SESSION

15:00-15:30	***Coffee***

Session 4: Potential scenarios to improve access to HPV vaccine and anticipated impact on allocation of doses and disease burden		
Question 3*: *What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could the enhanced HPV vaccine supply allocation be?		
15:30-16:00	Global supply scenarios for HPV vaccines	S. Malvolti
16:00-16:15	Questions for clarification	Plenary
16:15-17:00	Global vaccine demand: implications of different schedules (2 dose, extended intervals, with and without MACs) – unconstrained	E. Nickels
	Global supply-demand balance under different scenarios and implications for supply allocation	T.Cernuschi
17:00-17:30	Questions for clarification	Plenary
17:30–18:00	Summary of Day 1	Chairperson
18:00	***Closure of the Day 1 – Cocktail reception***	

Day 2: Friday 7 June 2019

Chair: Rakesh Aggarwal

Session 5: Potential strategies to achieve more equitable allocation of HPV vaccine under supply constraints		
Question 4: In light of the above conclusions/inputs how should HPV vaccine introduction be prioritized with respect to impact and feasibility?		
08:30–09:30	Impact on burden of disease by allocation scenario/strategy	M. Brisson/ K. Perm
09:30-10:30	Questions for clarification/Discussion	Plenary
10:30–11:00	***Coffee***	
11:00–11:45	Preliminary views on feasibility and acceptability of an off-label HPV vaccine schedule recommendation: – Feedback from NITAGs and EPI managers	P Bloem
11:45–12:30	Questions for clarification	Plenary
12:30-13:00	What are the knowledge gaps and what research and innovations could help to address them?	Plenary
13:00-14:00	***Lunch***	

Day 2: Friday, 7 June 2019

Chair: Rakesh Aggarwal

CLOSED SESSION – ONLY FOR WORKING GROUP MEMBERS

14:00–17:30	**Proposed conclusions and recommendations for SAGE consideration**	
14:00–15:00	**Conclusions on the questions discussed** *Question 1:* What is the current HPV vaccine uptake and what are the main barriers for access to HPV vaccines (national policy, economic, acceptability, vaccine doses access other)? *Question 2:* What does current evidence show on the immunogenicity and efficacy of a single dose of HPV vaccine and different intervals between the first and second doses of HPV vaccine? And what are the risks of bias of these studies? *Question 3:* What are the potential demand scenarios and the supply of HPV vaccines (short and mid-term outlook) and what could the enhanced HPV vaccine supply allocation be? *Question 4:* In light of the above conclusions/inputs, how should HPV vaccine introduction be prioritized with respect to impact and feasibility?	SAGE WG Members
15:00-15:30	Proposed recommendations for SAGE consideration	SAGE WG Members
15:30-16:00	***Coffee***	
16:00–17:00	Content of SAGE background document and evidence-to-decision tables to support proposed conclusions and recommendations Next steps	SAGE WG Members
17:30	**Closure of meeting**	