Strategic Advisory Group of Experts (SAGE) on Immunization

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

Background Document and Report to SAGE

March 2022

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2 Executive summary

2.1 Objectives of the reconvened 2021/2022 SAGE HPV Working Group

- To review the evidence for optimization of HPV vaccination schedules
- To discuss and propose additional research related to HPV vaccines and immunization to address evidence gaps.

2.2 Questions considered by the Working Group

- What evidence gaps exist and what research is recommended to enable SAGE to make a universal one dose HPV schedule recommendation?
- Should an off-label, permissive one-dose HPV vaccine schedule for use in multi-age cohort (MAC) catch up strategies be recommended?
- Should an off label, permissive one dose HPV vaccine schedule for use in the routine cohorts be recommended?

2.3 Summary recommendations

- To achieve the goals of the global strategy for cervical cancer elimination, SAGE recommends HPV vaccination for the primary target of 9-14-year-old girls, prior to sexual debut. National immunization programmes can use either a two-dose or a single-dose vaccination schedule.
- The option of a single-dose HPV vaccination schedule for routine and multi age cohort (MAC) catch-up vaccination in the primary target population is based on the very high vaccine efficacy of a single dose of HPV vaccine (97.5%) in girls up to 20 years of age observed in a high-quality RCT.
- This off-label option is recommended from a public health perspective because it provides comparable and high levels of individual protection, while being more efficient (fewer doses per cancer case prevented), easier to implement and less resource-intensive than a two-dose schedule. Modelling based on a single dose schedule predicts that the possibility of reaching a larger number of girls more rapidly and the resulting herd protection would compensate for any theoretical marginal difference in efficacy compared with two doses and has the potential to avert more cases of cervical cancer.
- A single-dose schedule can be considered for HPV vaccine products for which satisfactory efficacy and/or immunobridging data for a single-dose schedule are available. New and pipeline vaccines should generate evidence on peak and 24-month immunogenicity bridged to vaccines with proven single-dose efficacy.
- Since the single-dose efficacy data comes from a RCT and post RCT follow-up study involving girls up to age 20 years, either a two-dose or one-dose schedule can also be used for the vaccination of those who are 15-20 years old.
- For those older than 20 years, a reduced, two-dose schedule (instead of 3 doses previously) with a minimum interval of 6 months between doses can be used. Data on immunogenicity and efficacy from a post RCT follow-up study gives confidence that this reduced-dose schedule will provide protection.

- It is uncertain whether immunocompromised individuals will be protected adequately by reduced dose schedules. Until further evidence is available, immunocompromised persons, irrespective of age, should be prioritized and should receive at least two doses but ideally three doses if programmatically feasible.
- SAGE recommends, as a priority, adequately powered trials with reduced dose schedules in immunocompromised individuals to generate evidence on the immunogenicity, efficacy and duration of protection, including on the serum antibody titre response in individuals who have received a single-dose HPV vaccine prior to HIV seroconversion.
- Additional evidence should also be generated on reduced-dose schedules in boys and older females and males, and implementation research carried out to improve HPV vaccine coverage.
- For global equity, and considering the improving supply situation, SAGE recommends all countries urgently introduce the HPV vaccine for the primary target of 9-14-year-old girls and, where feasible and affordable, to prioritize catching-up missed girls through multi-age cohort (MAC) vaccination. Introducing the vaccination of boys and older females should be postponed until the global supply situation is fully unconstrained.

Implementation consideration

- SAGE is deeply concerned about the stagnating pace of introductions, the low HPV vaccine coverage in many countries and the gap with the 2030 target of 90% coverage needed for elimination. The primary aim of the HPV vaccination programme should be to reach the highest level of population protection and vaccine coverage among girls before they reach 15 years of age with at least one dose of HPV vaccine, irrespective of the schedule. Multiple opportunities should be created to allow girls at any age before 15 years to receive at least one dose and to implement MAC vaccination catch-up to ensure the highest possible population protection.

3 Background

Prophylactic HPV vaccines have now been in use for 15 years, during which time they have been demonstrated to have an excellent safety profile in population use[1] and very high efficacy against targeted type HPV infection and HPV-related diseases including cervical cancer.[2] WHO has recommended their use in pre-adolescent girls for the prevention of cervical cancer since 2009[3], initially using the originally trialled three dose schedule and, from 2014, in a two dose schedule (based on immunobridging data) for those aged under 15 at dose one[4]. Having previously considered evidence demonstrating that multi age cohort catch up vaccination at vaccine launch accelerates the time to disease reduction benefits, WHO recommends countries implementing HPV vaccination do so by vaccinating a routine targeted cohort of girls aged 9-14 years and providing a one year catch up program (to age 18, though for GAVI countries this is practically capped at age 15 due to the current scheduling requirements for 3 doses beyond age 15 years).[5] However, HPV vaccine supply has been insufficient to meet demand since 2018.

In October 2018, SAGE reviewed the evidence relating to the immunogenicity and efficacy of a single HPV vaccine, given the hypothesis that it may be sufficiently immunogenic to provide protection against HPV infection and disease, and in the context of the limited HPV vaccine supply, inequities in distribution of the supply and the challenges faced by many countries in administering a complete course of HPV vaccine. At that time, the evidence did not support the implementation of a universal one dose strategy and SAGE made the following recommendations to address the use of the vaccine in the context of restricted supply:[6]

- Countries should temporarily postpone implementation of boys, older age group (>15 years) and multi-age cohort HPV vaccination strategies until all countries have access to HPV vaccine. This will significantly relieve supply constraints in the short term and enable allocation of doses to high-burden countries currently planning to introduce this vaccine.

Alternative strategies:

- In order to retain the disease impact of MACs, target an older cohort of girls (e.g., those who are 13 or 14 years old or in a higher school grade)
- In order to reduce vaccine supply needs, adopt a “1+1” schedule with an extended interval of 3-5 years between doses for younger girls (e.g., 9 or 10 years old or lower school grade)

In 2021/2022 the HPV vaccine supply situation remains constrained and the introduction and routine delivery of HPV vaccination has been further adversely impacted by the COVID-19 pandemic.[7] However the first data from the multiple studies implemented to definitively assess the potential for single dose HPV vaccine to be a routinely recommended schedule were published in 2021. Therefore, the SAGE HPV Working Group was reconvened in April 2021 to reassess the status of the evidence supporting a single dose HPV vaccination strategy, identify whether further advice for optimising the use of available HPV vaccine doses can be made at this time and identify remaining research needs. The Working Group membership, Terms of Reference and meeting agendas can be found in the Appendix.

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[1] https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines
[2] Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338.
[3] Human papillomavirus vaccines WHO position paper. Wkly Epidemiol Rec, 84 (15) (2009), pp. 118-131.
[4] Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec, 89 (43) (2014), pp. 465-492;
[5] Human papillomavirus vaccines: WHO position paper., Wkly Epidemiol Rec 92 (2017), pp. 241–268.
[6] Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and Recommendations. Wkly Epidemiol Rec 93 (2019),pp 661-680.
[7] UNICEF/WHO vaccine coverage report at https://data.unicef.org/resources/dataset/immunization/

4 Current status of HPV introduction, coverage and supply

4.1 Global HPV vaccine coverage and introductions

A total of 116 countries (60%) have introduced HPV vaccine; this includes 5 countries with new introductions in 2021, which is fewer than in the peak year 2019 (n=18). (Figure 1) The smaller number of new introductions was likely influenced by supply constraints. Covid has impacted coverage rates for all vaccines, but the 2% global coverage drop seen with HPV (from 20% dose 1 coverage in girls in 2019 to 18% in 2020, and 15 to 13% completed course coverage) is relatively larger than the coverage drops for other vaccines. An estimated 2 million more girls missed their second dose in 2020 compared to 2019. The dropout rate for HPV vaccine has historically been high, fluctuating between 20% and 30% globally over the last decade.

HICs were relatively more resilient to Covid impact than lower income countries. The worst affected regions were AFR and AMR. (Figure 2) Country level impacts were variable and school-based programmes saw bigger declines than primarily health facility-based programmes.

Whilst 60% of countries have introduced HPV vaccine, 60% of the global burden of disease is in countries that have NOT yet introduced it. (Figure 3) Enabling MACs at the time of introduction in these countries could have a large impact, in particular in populous countries There is particular scope for MACs in 50 GAVI countries and in 34 remaining self-financing MICs that have not yet introduced and which have 25% of the global cohort of girls.

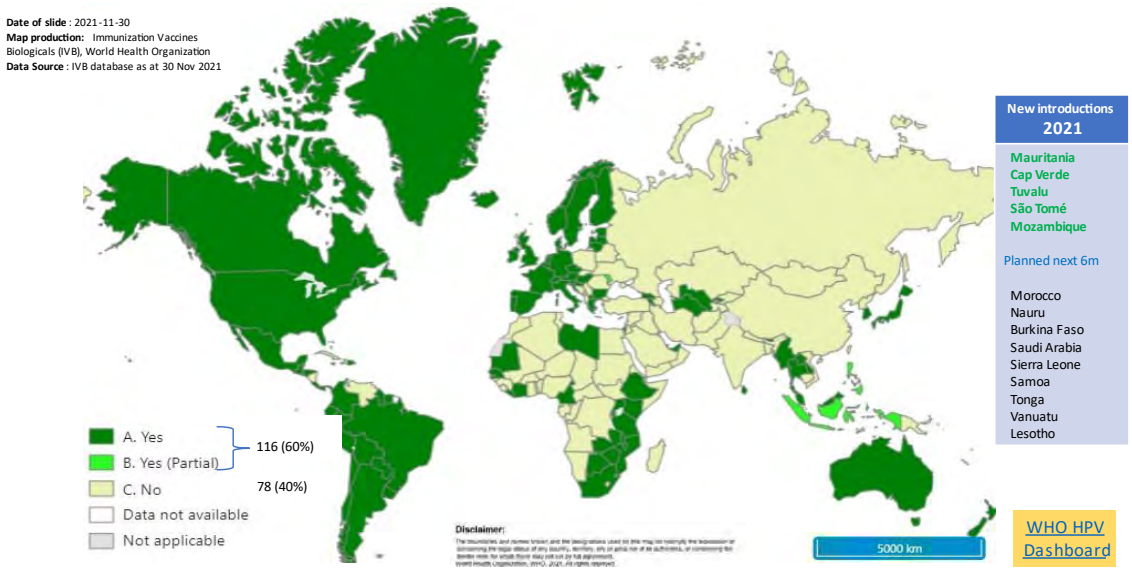


Figure 1: HPV vaccine introductions (as at 30 Nov 2021)

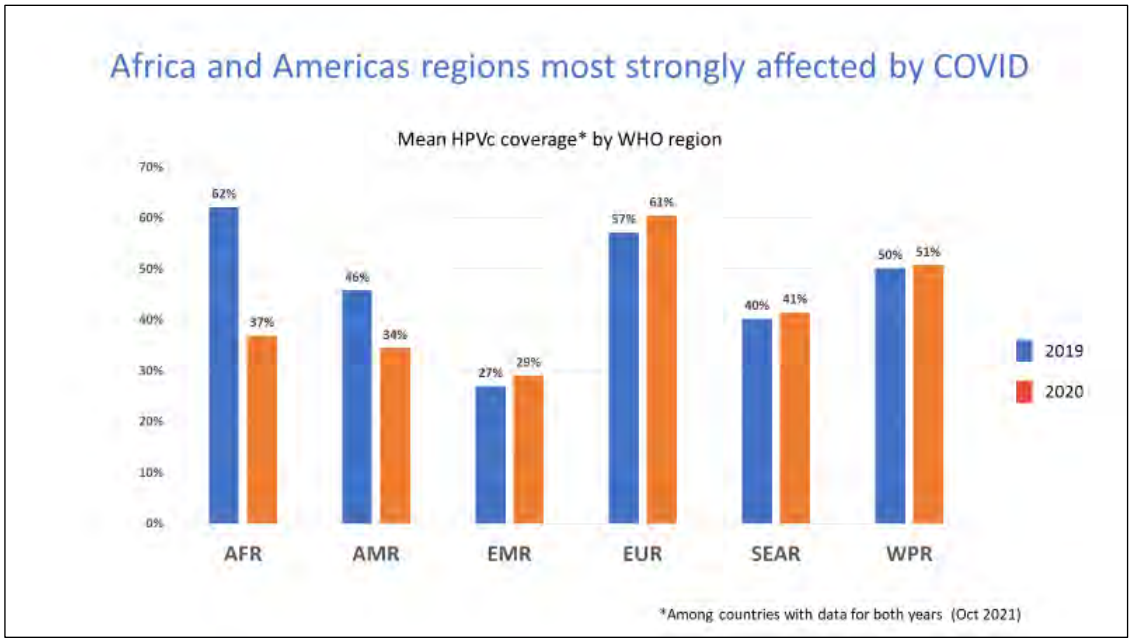


Figure 2: Mean HPV vaccine coverage (completed course) 2019 and 2020 by WHO region

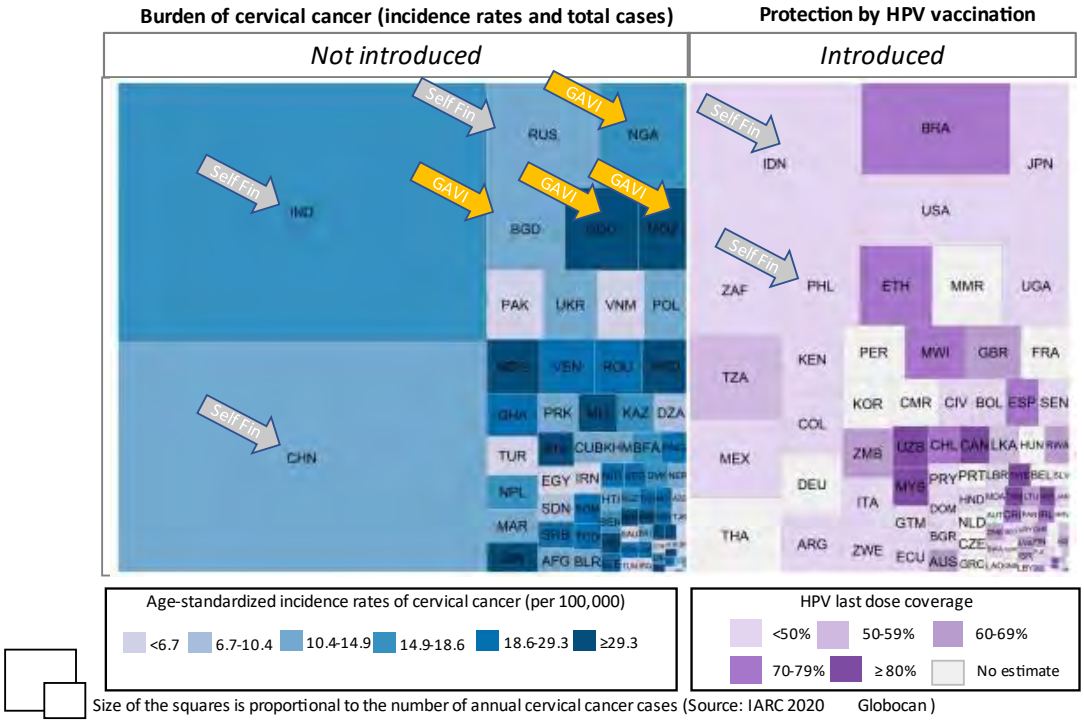


Figure 3: Country specific cervical cancer burden in non introduced countries and coverage in introduced countries (as at Dec 2020). *Arrows (yellow=GAVI countires, grey=self financing MICs) indicate substantial remaining opportunities for MACs in relation to population size and disease burden.*

4.2 Current HPV vaccine supply and projections

As of 28 Feb 2022, there are currently three HPV vaccine manufacturers with vaccines that have received marketing authorisation in at least one country; four products are available (2vHPV GSK, 4vHPV and 9vHPV Merck, 2vHPV Innovax). Three additional companies have products in late-stage clinical development (phase III) – 1 with 2v and 2 with 4v – those companies have been included into the supply forecast.

Whilst supply grew about 15% per year in recent years, this has remained insufficient to meet demand. Much larger increases are expected in the next 6 years with availability increasing to 1.8 times the current level in the next 1-3 years, 3.5 times in the medium term (4-6 years), and 3.6 times in the long term (7-9 years). (Figure 4). However, there are uncertainties about products in the pipeline, scale-up capacity and time to market. In the mid-long-term, available supply will increase significantly, driven by the outcome of manufacturers' development/scale-up efforts, with the ultimate size of the increase to be influenced by country preferences and acceptance of different products. 9 valent HPV vaccines are expected to become dominant in the second half of the decade with the entrance of up to 4 new manufacturers.

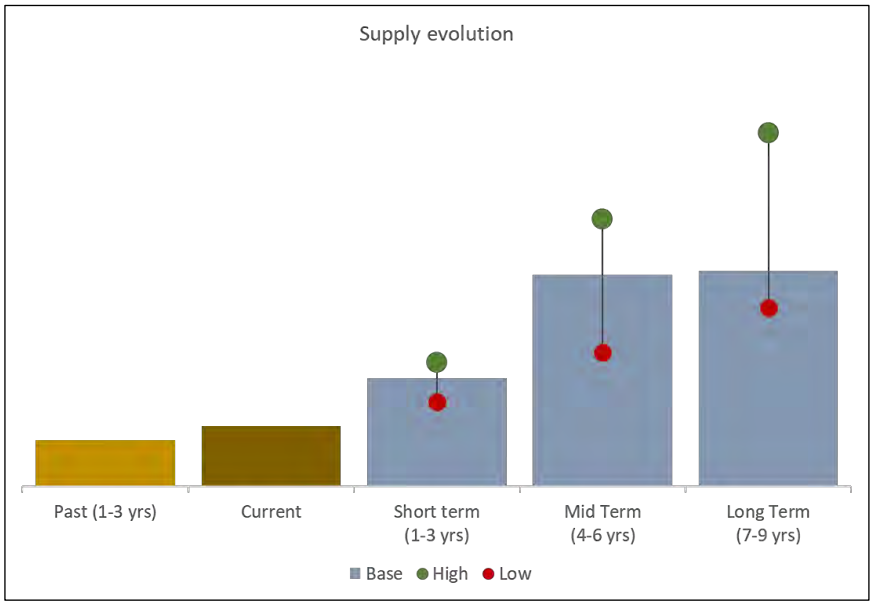


Figure 4: Projected HPV vaccine supply evolution

Global demand has grown throughout the last decade with an acceleration in 2018-2019 to approximately 60 M doses. Demand is expected to start recovering in 2022 post pandemic.

Several demand forecast scenarios were presented to the WG including the base case of 2 dose without MACs; a 2 Dose with MACs; and a single dose with MACs. It was noted that demand will not be halved in the one-dose scenario due to higher anticipated coverage. Countries switching to one-dose schedules may consider adoption of both sex schedules, which would have an impact on global demand. Key findings for the currently recommended strategy (2 doses and MACs) and the proposed alternative strategy, 1 dose with 1 dose MACs, are presented in Figures 5 and 6. Notably the current two dose strategy results in a projected peak demand of 136 million doses in 2028 before stabilising around 123 million in 2031. A one dose strategy from 2025 would result in a forecast of 70 million doses per annum from 2028.

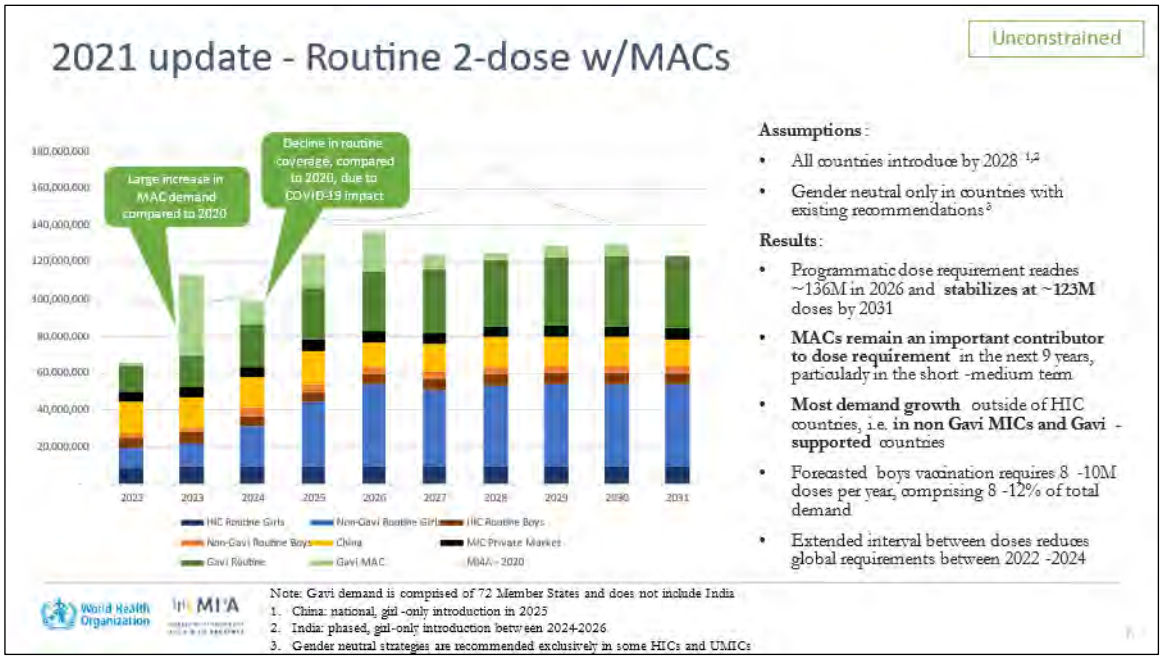


Figure 5: Projected HPV vaccine demand with a 2-dose strategy

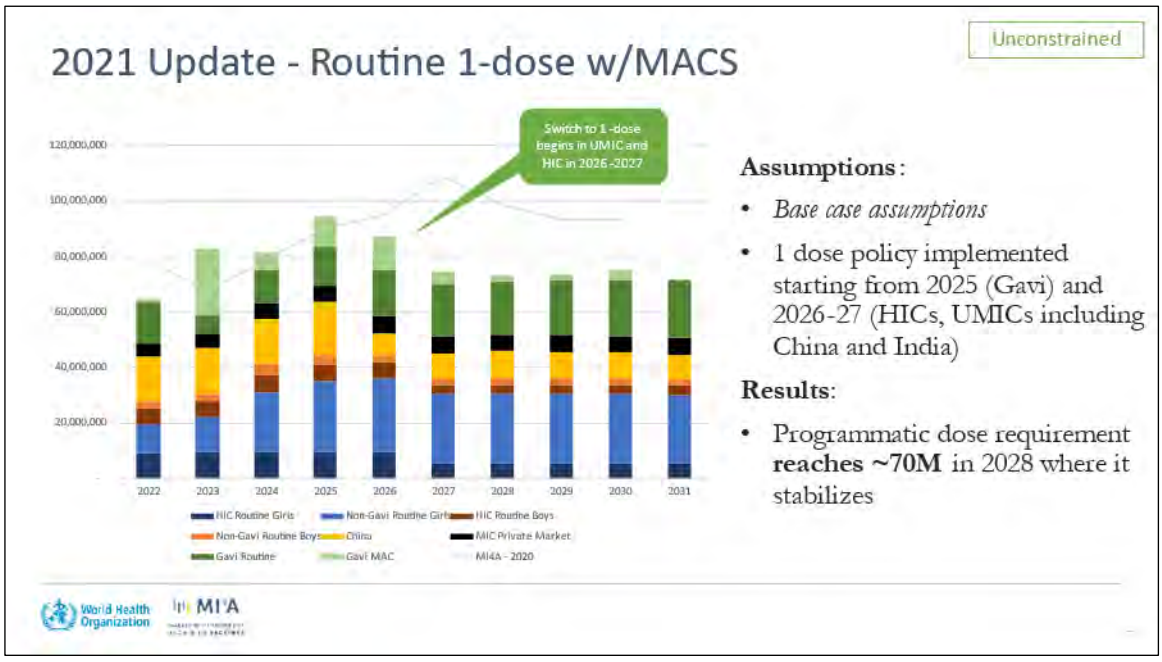


Figure 6: Projected HPV vaccine demand with a 1 dose strategy

As shown in Figure 7, **for all scenarios in the base case, supply is forecasted to be sufficient in the mid-long term unless supply side problems occur (e.g., delays or changes in capacity increases and/or pipeline delay).** Importantly, these projections assume that supply is shared across all markets and not earmarked for HIC/profitable settings, and that countries accept products based on available supply without refusing any specific presentation.

Nevertheless, supply remains tight in the short term and needs to be carefully managed.

Risk factors that can affect the supply situation include i) country acceptance for all products irrespective of valency or country of origin, which is particularly key as new products are beginning to reach the market and ii) uncoordinated contemporary widespread adoption of both-sex policies (in particular with catch-up) in UMICs and China in the short term. Active management of supplier base is required in the long run, when significant excess supply is expected (from 2026-27), in order to avoid supply disruption and reduction of competition as result of potential unforeseen market exits.

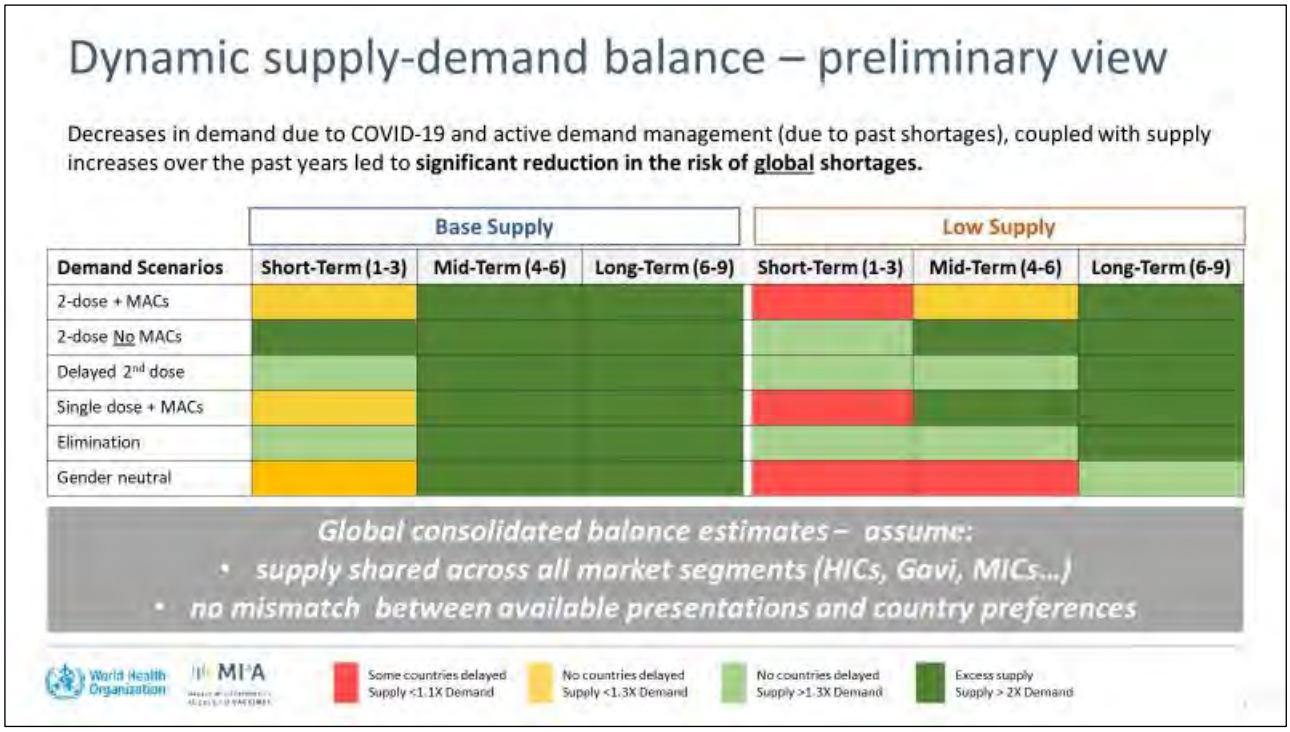


Figure 7: Projected supply-demand balance (6 scenarios) under base and low supply situations

5 Evidence reviewed: Updated one dose evidence: trials/interventional cohort studies

When previously reviewed in 2018, "*SAGE noted that, although use of a 1-dose schedule would facilitate the vaccine's use, there is insufficient evidence at this time to recommend it*."[8] As shown in Figure 8, data from several key trials investigating the immunogenicity and efficacy/effectiveness of a single HPV vaccine dose are now available. Major findings from four studies, and the Working Group's interpretation and assessment of the contribution of each to the evidence base, are outlined below.

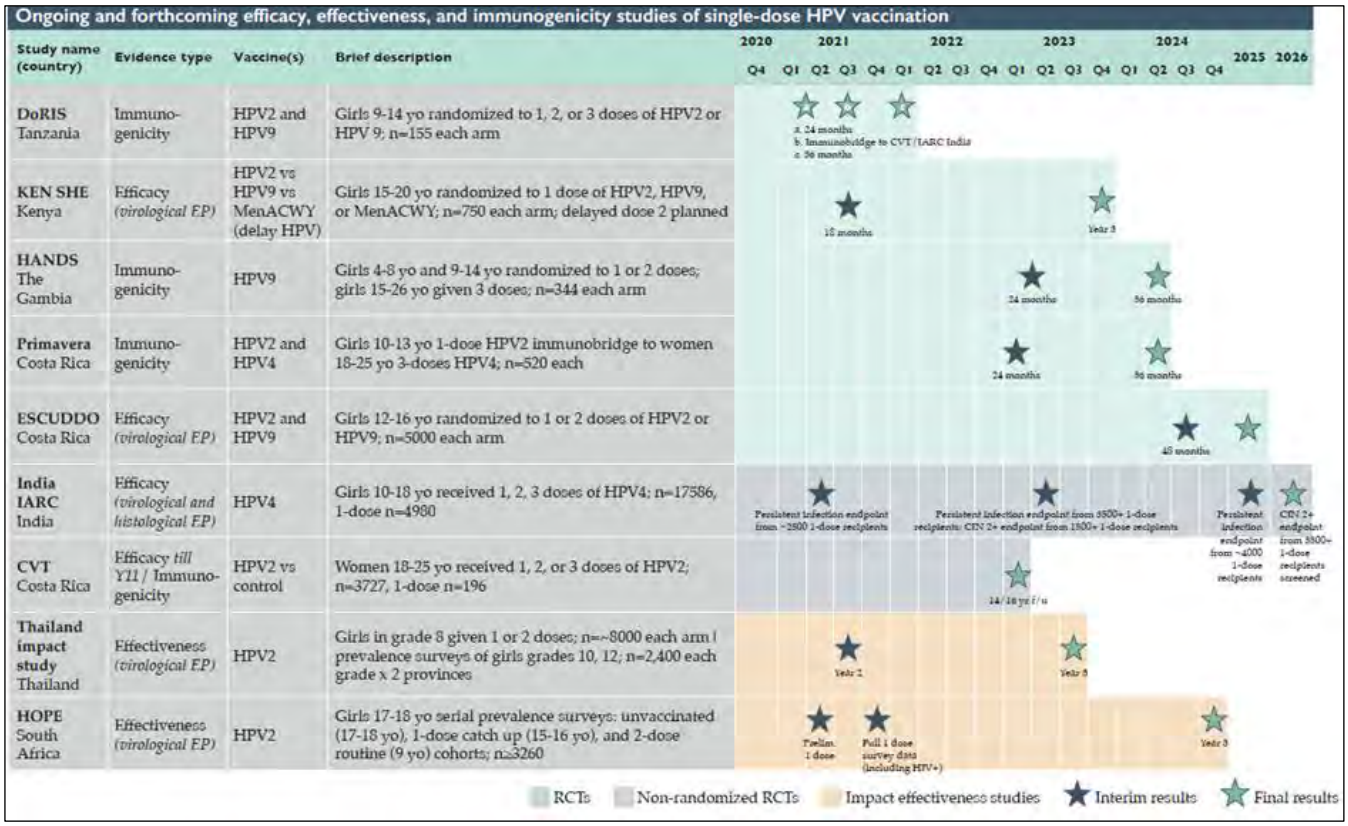


Figure 8: Summary table of ongoing single-dose HPV vaccination studies

5.1 KEN SHE 2vHPV and 9vHPV RCT

The primary objectives of this randomised, multi-centre, double-blind, controlled trial[9] were to:

- To test the efficacy of immediate single-dose nonavalent or bivalent HPV vaccination to prevent incident persistent HPV 16/18 infection

[8] Meeting of the Strategic Advisory Group of Experts on Immunization, October 2018 – Conclusions and Recommendations. Wkly Epidemiol Rec 93 (2019),pp 661-680.
[9] Barnabas RV, Brown ER, Onono MA et al. Efficacy of single-dose HPV vaccination among young African women [preprint] DOI:10.21203/rs.3.rs-1090565/v1

- To test the efficacy of immediate single-dose nonavalent HPV vaccination to prevent incident persistent HPV 16/18/31/33/45/52/58 infection

Methods: 2,275 15–20-year-old females were recruited in three centres in Kenya and had 1 to 5 partners, were HIV negative, and had no previous HPV vaccination. The three trial arms were immediate 9vHPV or immediate 2vHPV (with delayed meningococcal) or meningococcal (with delayed HPV) vaccine. Participants had a Pap smear at enrolment, baseline HPV test and serology, followed by HPV tests at 3, 6, 12 and 18 months plus month 18 serology. The primary analysis cohort was mITT (negative HPV DNA at enrolment/month 3 and negative baseline serology: n=1458 for 16/18 mITT cohort as 29% HPV exposed and n=615 for 16/18/31/33/45/52/58 mITT cohort as 52% HPV exposed). Sensitivity analyses additionally included i) participants who were seropositive at enrolment (sensitivity cohort) and ii) additionally excluded those who were HPV positive at 6 months (extended sensitivity cohort).

Results: At 18 months were: HPV 16/18 mITT VE 97.5% (CI: 81.7-99.7%) for both 9vHPV and 2vHPV. VE against 7 HR-types was 88.9% (CI: 68.5-96.1) with 9vHPV. For the sensitivity cohorts, VE against HPV16/18 9vHPV was 98.2% (CI: 86.6-99.7), 2vHPV 94.4% (CI:82.1-99.3) and extended sensitivity 100% VE. For the sensitivity cohort, the VE for the 7HR-types 9vHPV was 89.3% (CI:76.4-95.1), and for the extended sensitivity cohort was 95.0% (CI:67.1-99.9).

						95% Confidence Interval*		Statistical Comparisons***			
Arm	Enrolled (n)	HPV 16/18 naïve^ (mITT) (n)	Incident persistent HPV 16/18 (n)	Woman-years of Follow-up**	Incidence of persistent HPV 16/18 per 100 Woman-years	Lower Bound	Upper Bound	Comparison	Vaccine Efficacy	95% CI	P-value (Log-rank)
Nonavalent HPV	758	496	1	596.27	0.17	0.00	0.93	Nonavalent v. Meningococcal	97.49%	(81.66%, 99.66%)	<.0001
Bivalent HPV	760	489	1	589.38	0.17	0.00	0.95	Bivalent v. Meningococcal	97.48%	(81.60%, 99.65%)	<.0001
Meningococcal	757	473	36	527.35	6.83	4.78	9.45				

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.
**Follow-up time begins at 3 months and includes only women HPV 16/18 DNA-negative at month 0 and month 3, and antibody-negative at month 0.
***Hazard ratios with 95% confidence intervals are estimated using a single Cox proportional hazards regression model with a three-way class variable for vaccine arm. The model is stratified by site, with Efron method for handling ties, and vaccine arm was the only covariate. Vaccine efficacy and 95% CI computed from the hazard ratio as 100*(1-Point Estimate). P-value (log-rank) computed for each comparison using the log-rank test.
^ HPV 16/18 naive participants are those who tested negative for HPV 16/18 antibodies at enrollment and negative for HPV 16/18 DNA at enrollment and month three.

Table 1: Incidence of persistent HPV 16/18 and Vaccine Efficacy by Month 18 (mITT Cohort)

						95% Confidence Interval*		Statistical Comparisons***			
Arm	Enrolled (n)	HPV 16/18/31/33/45/52/58 naïve^ (mITT) (n)	Incident persistent HPV 16/18/31/33/45/52/58 (n)	Woman-years of Follow-up**	Incidence of persistent HPV 16/18/31/33/45/52/58 per 100 Woman-years	Lower Bound	Upper Bound	Comparison	Vaccine Efficacy	95% CI	P-value (Log-rank)
Nonavalent HPV	758	325	4	389.18	1.03	0.28	2.63	Nonavalent v. Meningococcal	88.91%	(68.45%, 96.10%)	<.0001
Meningococcal	757	290	29	307.81	9.42	6.31	13.53				

*Exact 95% confidence interval for incidence rate computed using the Poisson distribution.
**Follow-up time amongst women HPV 16/18/31/33/45/52/58 DNA-negative at month 0 and month 3, and antibody-negative at month 0.
***Hazard ratios with 95% confidence intervals are estimated using a single Cox proportional hazards regression model with a three-way class variable for vaccine arm. The model is stratified by site, with Efron method for handling ties, and vaccine arm was the only covariate. Vaccine efficacy and 95% CI computed from the hazard ratio as 100*(1-Point Estimate). P-value (log-rank) computed for each comparison using the log-rank test.
^ HPV 16/18/31/33/45/52/58 naive participants are those who tested negative for HPV 16/18/31/33/45/52/58 antibodies at enrollment and negative for HPV 16/18/31/33/45/52/58 DNA at enrollment and month three.

Table 2: Incidence of persistent HPV 16/18/31/33/45/52/58 and Vaccine Efficacy by Month 18 (mITT Cohort)

Interpretation:

The Working Group reflected that this is a ‘ a e chan i n ’ study as it was well conducted and found **strikingly high vaccine efficacy with one dose of HPV vaccine**. Separate analyses of VE against types 31/33/45/52/58 has not yet been undertaken noting that this is the first study to estimate overall 9vHPV efficacy directly (VE 88.9%), as in the original 9vHPV trial the results for HPV16/18 were immunobridged against historical controls (as the comparison group received 4vHPV).[10] In the original 9vHPV trial the VE for high grade disease caused by HR types 31/33/45/52/58 overall was 96.7%;(95% CI, 80.9 to 99.8) so this result is consistent although there is no direct comparison.

5.2 India IARC 4vHPV trial

The Working Group reviewed the latest available data from this Indian cohort study[11] which commenced in 2009 as a cluster RCT of 2 vs 3 doses 4vHPV in 10–18-year-old girls with loss of randomisation due to stopping in April 2010 leaving 4 groups: 3-dose, 2-dose per protocol, 2-dose default (at 0, 2 months), and single-dose default groups. As outlined in Figure 9, which gives an overview of the methods used to assess outcomes during follow up, control populations were recruited post-hoc as comparison groups for the vaccinated cohort.

The main aim of the latest analysis was to compare vaccine efficacy of single dose to that of three and two doses in protecting against persistent HPV 16 and 18 infection at 10 years post vaccination. Immunogenicity at 10 years was also examined.

[10] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015 Feb 19;372(8):711-23. doi: 10.1056/NEJMoa1405044.
[11] Lancet Oncol 2021: 22: 1518-29

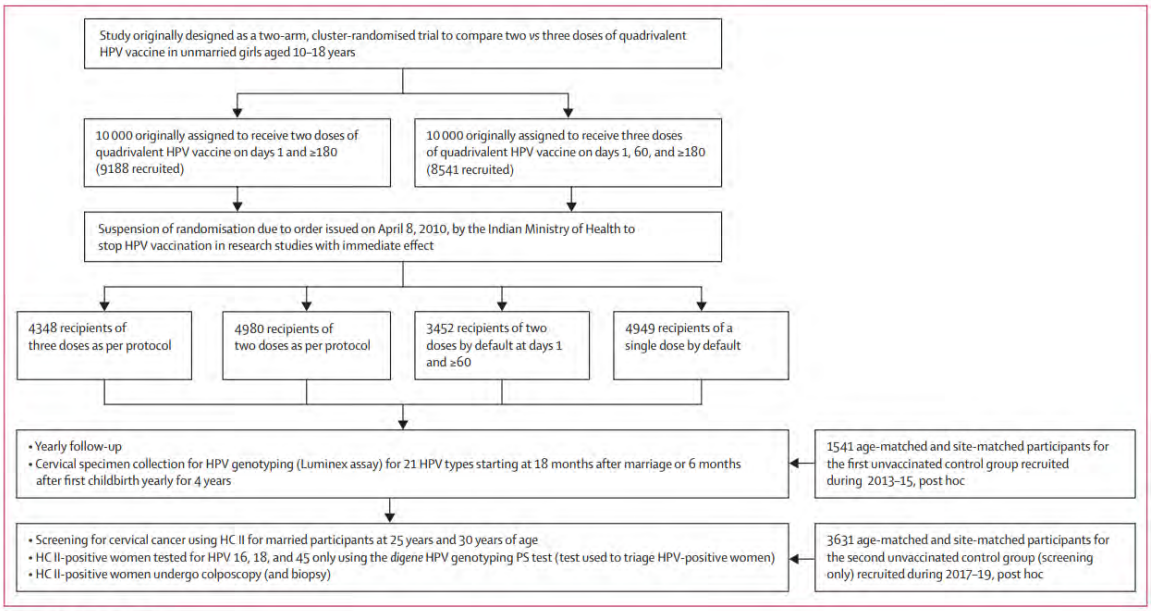


Figure 1: **Study flow chart**
HC II=Hybrid Capture II. HPV=human papillomavirus.

Figure 9: Study flow chart: IARC India cohort study[12]

Results

Immunogenicity: Although the antibody titres to HPV types 16/18 induced by a single dose were inferior, a 10-year immunogenicity analysis using M9 ELISA test showed a steady plateau for HPV types 16 and 18. 95.4% of one-dose recipients were still seropositive for HPV16 as were 41.7% for HPV18 (unpublished). In relation to equivalence of immune response to 2 doses (0,6 months) compared to 3 doses (0,2,6 months) across the 10-18-year-old age range, GMTs were equivalent in the 2 and 3 dose groups at 60 months (using a pseudovirion-based neutralisation assay (unpublished)) as previously seen using ELISA at 48 months.[13]

Efficacy: One-dose recipients had low rates of incident (3.1%) and persistent (0.1%) HPV 16/18 infection similar to the 2 (2.6%/0.1%) and 3 dose (2.9%/0.1%) groups. The unvaccinated control group (retrospectively recruited and non-randomized) had higher 16/18 infection rates (incident 9.7%, persistent 2.7%) and non-targeted HPV types than the vaccinated groups. However, compared to the vaccinated groups, these controls had a higher geographically based background HPV risk, differences in time between marriage and first specimen collection, and a larger number of samples collected to date, which were all determined to be significant predictors of non-vaccine type HPV infection. After adjustment for these three factors by the calculation of risk factor scores for each participant and the creation of risk strata (see Suppl. Annex in article), **VE against persistent HPV 16/18 infection was 91.2%/94.5%/94.2% for 3/2/1 doses, respectively.**

Interpretation

The Working Group discussed the imperfect control group in the study (recruited later and different characteristics); it noted that the 2 and 3 dose groups were also compared to this group, and that the similar absence of infection/disease across all 3 vaccinated groups is noteworthy, supporting vaccine effect. The sub-analysis of the Barshi area, where controls were more akin to the vaccinated girls than across the entire study population and which had a medium level of background infection, gave consistent findings.

[12] Lancet Oncol 2021: 22: 1518-29
[13] Lancet Oncol 2016; 17: 67–77

Data disaggregated for HPV 16/18 incident and persistent infection outcomes were additionally presented and shown to be consistent with the overall findings.

The Working Group discussed whether the 42% HPV18 seropositivity in the single-dose arm at 10 years was of concern. It was noted that the cut-off used for seropositivity is arbitrary and levels being measured are substantially above the limit of detection. Merck HPV18 cLIA always gives a lower Ab measure than HPV16, noting that the neutralizing epitope chosen for the cLIA HPV 18 is not dominant in the general female population[14], but is not associated with breakthrough disease. It was noted that in animal studies that protection against cervicovaginal challenge was seen at antibody levels far below the limits of detection and that very low levels of antibody in the tissue appear to be protective. The importance of antibody kinetics was noted, with consistent evidence indicating a lack of ongoing decay in the plateau phase being very encouraging for long-term protection.

5.3 DoRIS trial - Dose Reduction Immunobridging & Safety Study of 9vHPV and 2vHPV in Tanzanian girls

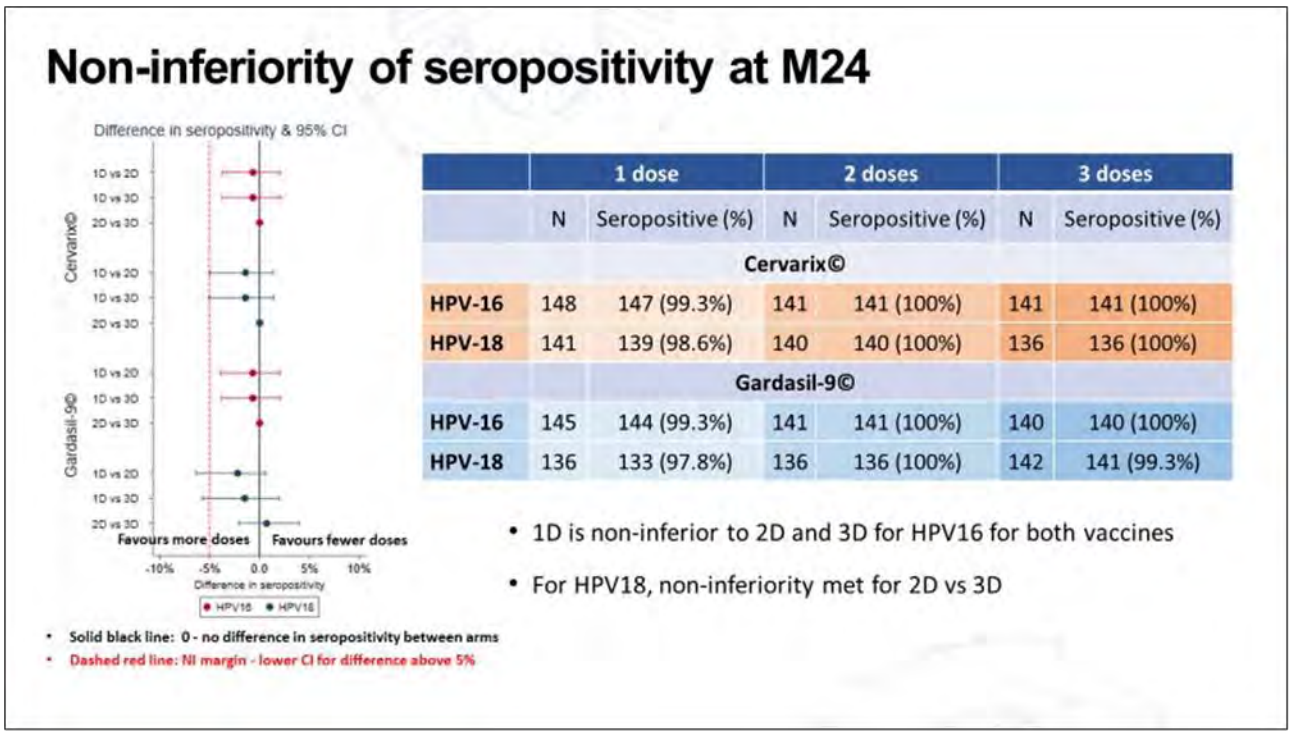
Month 24 results of this 9vHPV and 2vHPV unblinded study of 1,2,3 doses that assessed immunogenicity and safety were presented. The study included 930 girls 9-14 years in 6 arms (155 in each arm) and is the first trial of one dose in the target age group, with the primary objectives to

- Demonstrate non-inferiority of HPV 16/18 seroconversion after 1 dose compared with 2 or 3 doses of same vaccine at M24
- Primary immunobridging objective: Demonstrate non-inferiority of HPV 16/18 antibody GMT at M24, comparing 1 dose in DoRIS with historical efficacy cohorts who received only 1 dose (CVT, India-IARC).

Results

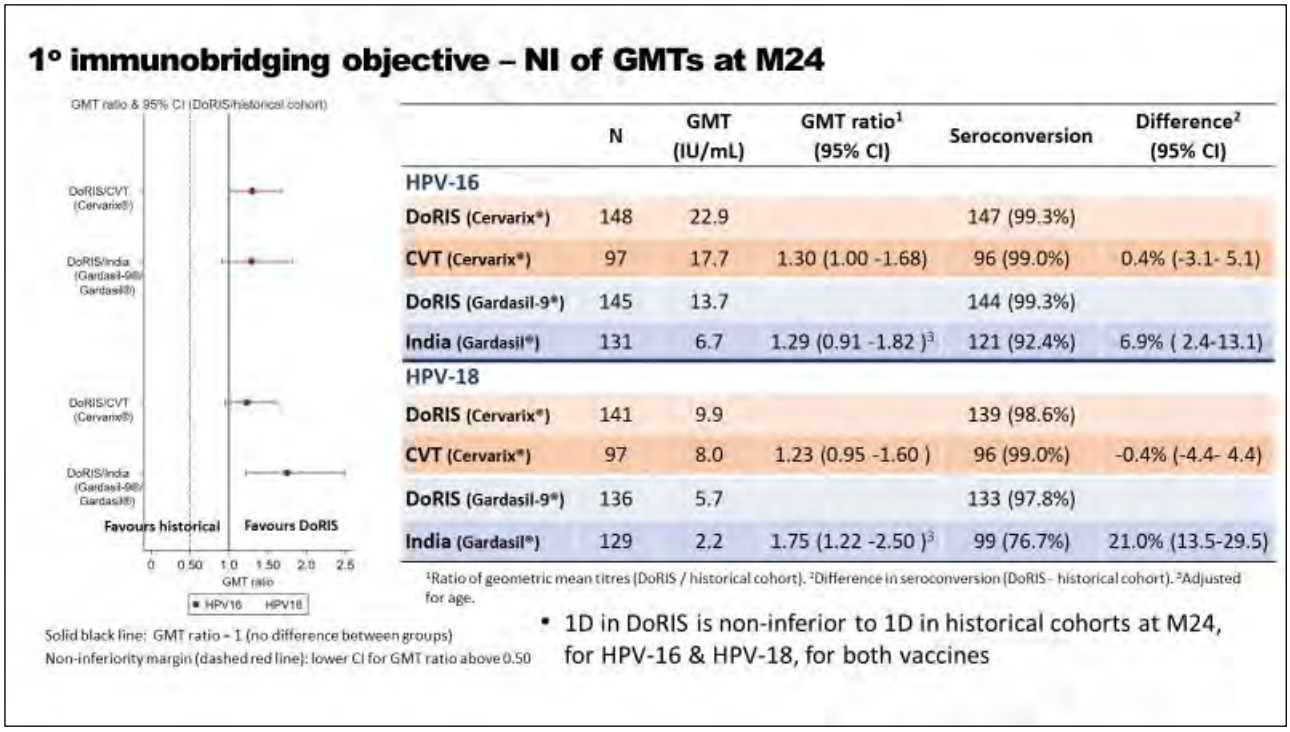
The study found that 1 dose was non-inferior for HPV16 seropositivity at month 24 for both 2vHPV and 9vHPV. For HPV18, the non-inferiority criterion was met for 2vHPV but not for 9vHPV. (Figure 10) Antibody avidity was similar across doses for HPV16 and 18 for both the vaccines. Plateau titres for the one dose group were stable between month 12 and month 24 for both 2vHPV and 9vHPV. In immunobridging to CVT and India studies, one dose in DoRIS was non-inferior to the historical cohorts at month 24 for both vaccines and for HPV16 and 18. (Figure 11)

[14] Brown DR, Garland SM, Ferris DG, et al. The humoral response to Gardasil over four years as defined by total IgG and competitive Luminex immunoassay. Hum Vaccin 2011; 7:230-8.



	1 dose		2 doses		3 doses	
	N	Seropositive (%)	N	Seropositive (%)	N	Seropositive (%)
			Cervarix©			
HPV-16	148	147 (99.3%)	141	141 (100%)	141	141 (100%)
HPV-18	141	139 (98.6%)	140	140 (100%)	136	136 (100%)
			Gardasil-9©			
HPV-16	145	144 (99.3%)	141	141 (100%)	140	140 (100%)
HPV-18	136	133 (97.8%)	136	136 (100%)	142	141 (99.3%)

Figure 10: Non-inferiority of seropositivity at month 24



	N	GMT (IU/mL)	GMT ratio[1] (95% CI)	Seroconversion	Difference[2] (95% CI)
HPV-16					
DoRIS (Cervarix®)	148	22.9		147 (99.3%)	
CVT (Cervarix®)	97	17.7	1.30 (1.00 -1.68)	96 (99.0%)	0.4% (-3.1- 5.1)
DoRIS (Gardasil-9®)	145	13.7		144 (99.3%)	
India (Gardasil®)	131	6.7	1.29 (0.91 -1.82)[3]	121 (92.4%)	6.9% (2.4-13.1)
HPV-18					
DoRIS (Cervarix®)	141	9.9		139 (98.6%)	
CVT (Cervarix®)	97	8.0	1.23 (0.95 -1.60)	96 (99.0%)	-0.4% (-4.4- 4.4)
DoRIS (Gardasil-9®)	136	5.7		133 (97.8%)	
India (Gardasil®)	129	2.2	1.75 (1.22 -2.50)[3]	99 (76.7%)	21.0% (13.5-29.5)

[1]Ratio of geometric mean titres (DoRIS / historical cohort). [2]Difference in seroconversion (DoRIS - historical cohort). [3]Adjusted for age.

Figure 11: Non-inferiority assessment of GMTs at month 24

Interpretation

The Working Group noted the issues surrounding seropositivity with dependence upon where the cut-off point is set and the sensitivity of the assay used. The Working Group noted that

seropositivity for HPV18 at month 24 (one vs other groups) was high and non-inferiority was just missed for Gardasil9 with the assay used.

5.4 Summary

The Working Group views the KEN SHE findings of very high protection against incident HPV infection in sexually active 15-20-year-olds with one dose of 2vHPV or 9vHPV as a critical finding. The study represents the highest quality evidence to date assessing vaccine efficacy after one dose of HPV vaccine compared to no vaccination. The Working Group notes that such a high efficacy estimate for one dose makes the awaited one vs two dose ESCUDDO data (2024) less critical, as it will be unlikely to be able to document a higher two dose efficacy with such a high expected one dose efficacy. The KEN SHE finding is highly congruent with the India cohort findings of extremely low incident HPV16/18 infection after one dose 4vHPV vaccine given at age 10-18 years and with the long term follow up of the Costa Rica Vaccine Trial among women originally vaccinated at 18-25 years of age old, which continues to show high and equivalent one dose efficacy comparable to the three dose group and a stable antibody plateau in the one dose group now out to 11 years.[15] [16] The immunogenicity data from DoRIS strongly supports, as expected, that one dose will be as efficacious in the routinely targeted younger age cohort as in the cohorts assessed in studies to date.

[15] Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. J Natl Cancer Inst. 2020 Oct 1;112(10):1038-1046. doi: 10.1093/jnci/djaa011.

[16] Tsang SH, Sampson JN, Schussler J, et al. Durability of Cross-Protection by Different Schedules of the Bivalent HPV Vaccine: The CVT Trial. J Natl Cancer Inst. 2020 Oct 1;112(10):1030-1037. doi: 10.1093/jnci/djaa010.

6 Evidence reviewed: updated systematic review

The Working Group reviewed the findings of the updated Cochrane systematic review (updated from Feb 2019 through to Jan 2022). The review now includes 4 HPV vaccines, 3 comparisons (0 vs 1 dose, 1 vs 2 doses and 1 vs 3 doses) and multiple outcomes. It utilises an updated risk of bias tool (v2.0) for RCTs and the ROBINS-I tool for non-randomised studies. The 59 studies include 4 RCTs, 4 post hoc analyses of RCTs, 1 single arm trial and 50 observational studies, of which 24 are new since the previous review. Only 2 studies included one dose efficacy outcomes for males and 4 studies included data for both females and males. There are 36 4vHPV, 11 2vHPV, 12 mixed studies, and 1 study of 2vHPV Innovax. Overall risk of bias ranged from low to some concerns for RCTs, mostly moderate for post-hoc RCT follow-up studies, and *mostly serious to critical for observationa*l, although there were some observational studies at moderate risk of bias because they measured and controlled for the most important confounders. This summary presents the main findings of note in relation to the recommendations of the Working Group, that is the new higher quality evidence facilitating the support of a permissive one dose recommendation. For further details, please refer to the Cochrane review document.

6.1 Summary of findings 0 vs 1 HPV vaccine dose

The key findings were evidence of high one dose efficacy against targeted type HPV infection with 2vHPV and 9vHPV from the KENSHE trial, and for 4vHPV from the India IARC study 10 year follow up.

Immunogenicity

- There was high certainty evidence that one dose of HPV vaccine resulted in higher GMTs for HPV 16 and 18 than no vaccine and this was sustained for up to 5 years.
- There was high certainty evidence that one dose of HPV vaccine resulted in higher seropositivity to HPV 16 and 18 than no vaccine and this was sustained for up to 11 years.

HPV infections

- There was high certainty evidence that one dose HPV vaccine resulted in a large reduction in persistent HPV 16/18 infections compared with no vaccine over the short term (up to 18 months follow-up).

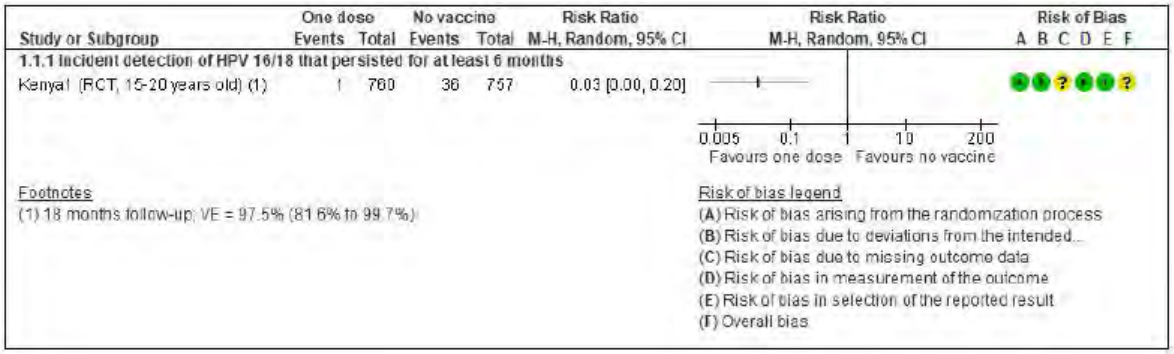


Figure 13: Persistent HPV infections following bivalent vaccine (Cervarix) – RCT 1 vs 0 doses

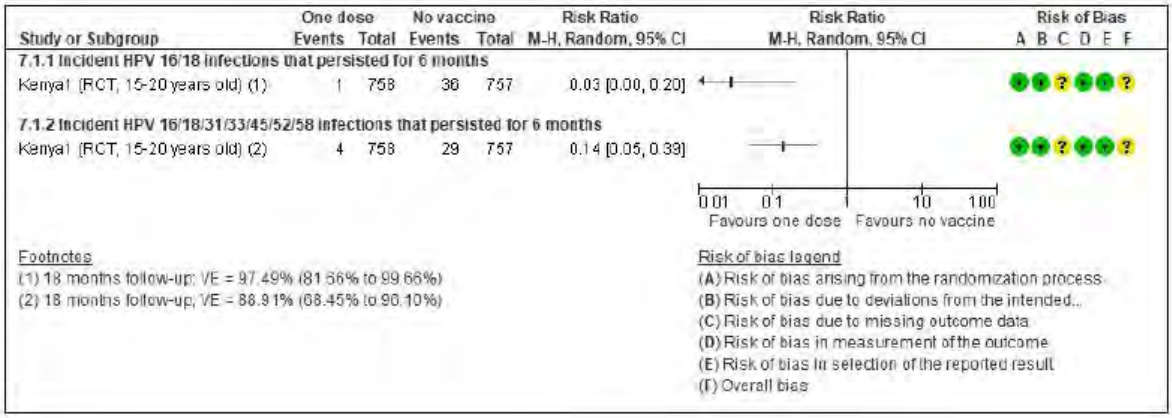


Figure 14: Persistent HPV infections following nonavalent vaccine (Gardasil9) – RCT 1 vs 0 doses

- There was moderate certainty evidence that one dose HPV vaccine resulted in a reduction in persistent HPV 16/18 infections compared with no vaccine over the long term (up to 10 years).

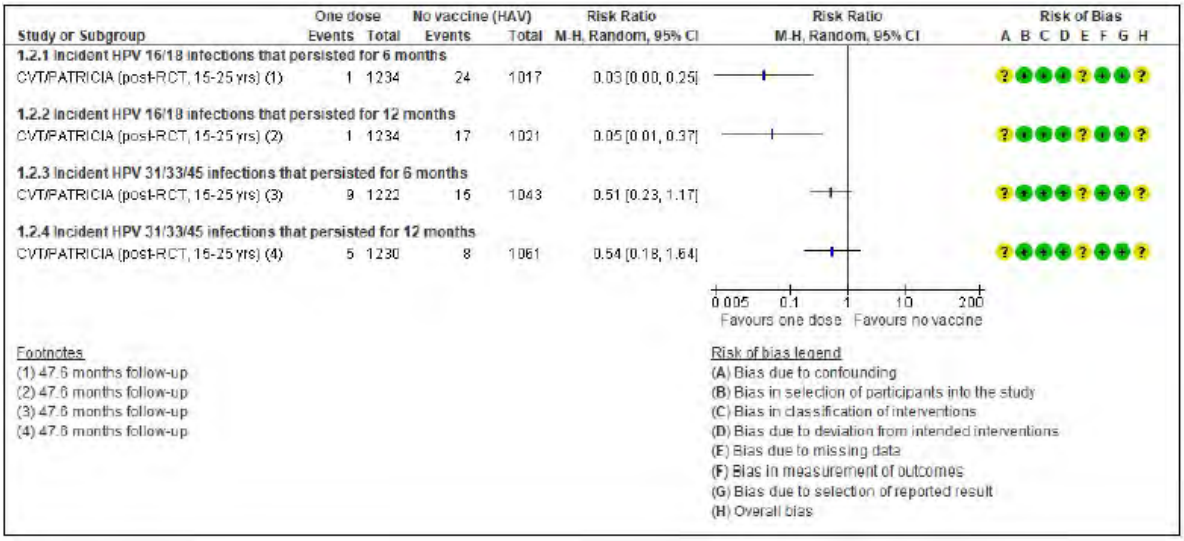


Figure 15: Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 0 doses

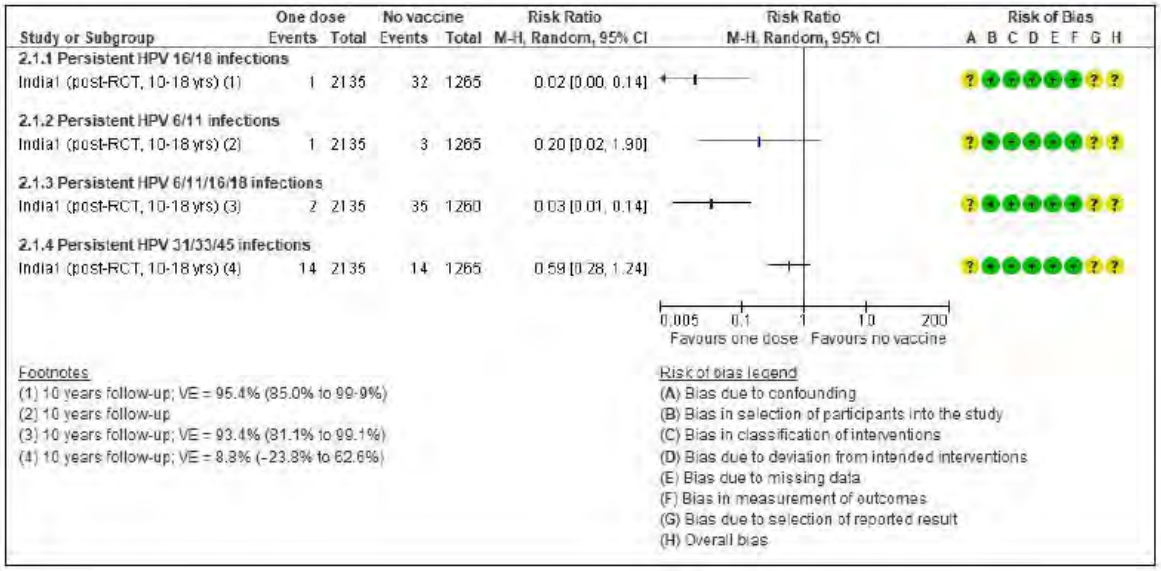


Figure 16: Persistent HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses 1 vs 0 doses

- The evidence suggested that one dose of HPV vaccine may reduce prevalence of HPV as well as incident HPV infections compared with no vaccine.

Other clinical outcomes

- Evidence suggests that one dose of HPV vaccine may reduce the incidence of genital warts compared with no vaccine, but this is based on observational studies at serious risk of bias.
- Evidence on one dose of HPV vaccine on the incidence of abnormal cytology or CIN is limited and based on observational studies at serious risk of bias.
- Estimates of effect on clinical outcomes from observational studies were affected by the age of participants and the length of the buffer period used.

The GRADE summary of evidence is presented below.

Certainty assessment						Nº of patients		Effect		Certainty	Comments
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: short term follow-up, 18 months											
1 RCT	not serious[1]	not serious	not serious	not serious[2]	none	2/985 (0.2%)	36/473 (7.6%)	**RR 0.03** (0.01 to 0.11)	74 fewer per 1000 (from 75 fewer to 68 fewer)	⊕⊕⊕⊕ High	Kenya1 (KEN-SHE), bivalent (Cervarix) and nonavalent (Gardasil 9), 15-20 years old at vaccination
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[3]	not serious	not serious	not serious[2]	none	2/3369 (0.1%)	56/2282 (2.5%)	**RR 0.03** (0.01 to 0.10)	24 fewer per 1000 (from 24 fewer to 22 fewer)	⊕⊕⊕◯ Moderate	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMTs following one dose ranged from 5.73 to 320.43.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMT following one dose ranged from 4.79 to 81.92.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1

CI: confidence interval; **HPV:** human papillomavirus; **RCT:** randomized controlled trial; **RR:** risk ratio

1. Not downgraded despite some concerns with missing outcome data, estimates from unpublished data of modified intention-to-treat analysis of participants HPV naive at baseline.
2. Not downgraded for imprecision due to large effect estimates, despite few events.
3. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.

Table 3: GRADE evidence profile for single dose HPV vaccine compared with no vaccine for HPV infection, seroconversion and antibody titres

6.2 Summary of findings 1 vs 2 or 3 HPV vaccine doses

The key findings were that, whilst the immunogenicity of 2 or 3 doses is superior to one, high seropositivity is observed after one dose with all vaccines. The efficacy of two doses is not clearly superior to 1 and there was no difference in efficacy of 3 compared to 1 dose against 16/18 HPV infection (or cross protection against infection with 31/33/45) from the Costa Rica or India studies. More variation was seen in observational studies.

Immunogenicity

- There was high certainty evidence that one dose of HPV vaccine resulted in lower GMTs for HPV 16 and 18 than two or three doses and this was sustained for up to 5 years.
- There was high certainty evidence that one, two or three doses of HPV vaccine resulted in similarly high rates of seropositivity to HPV 16 and 18 and this was sustained for up to 11 years.

HPV infections

- There was low certainty evidence that one dose of HPV vaccine resulted in little to no difference in persistent HPV 16/18 infections compared with two or three doses.

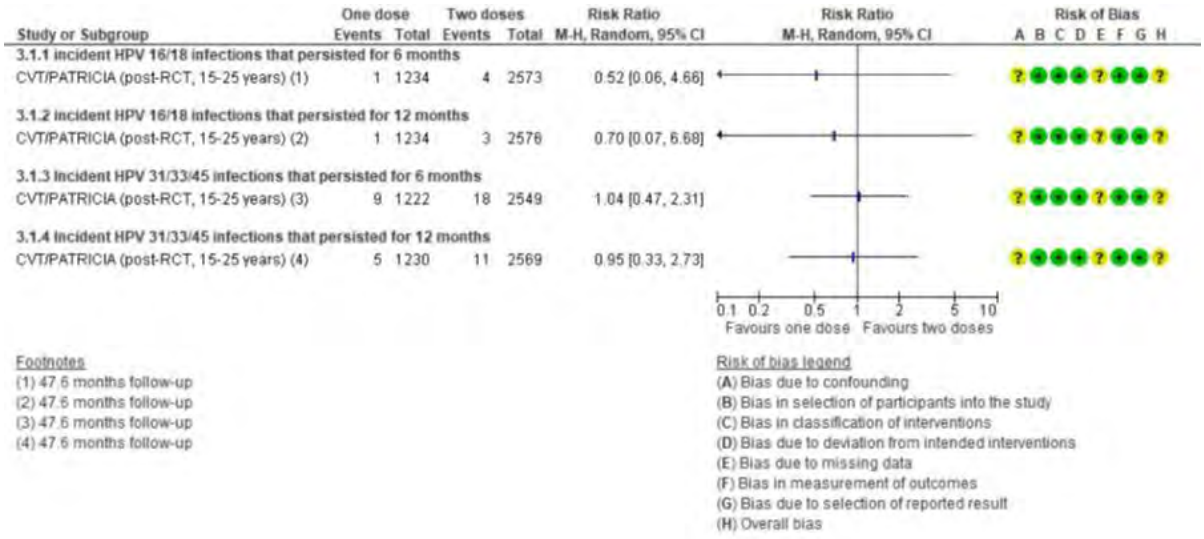


Figure 17: Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 2 doses

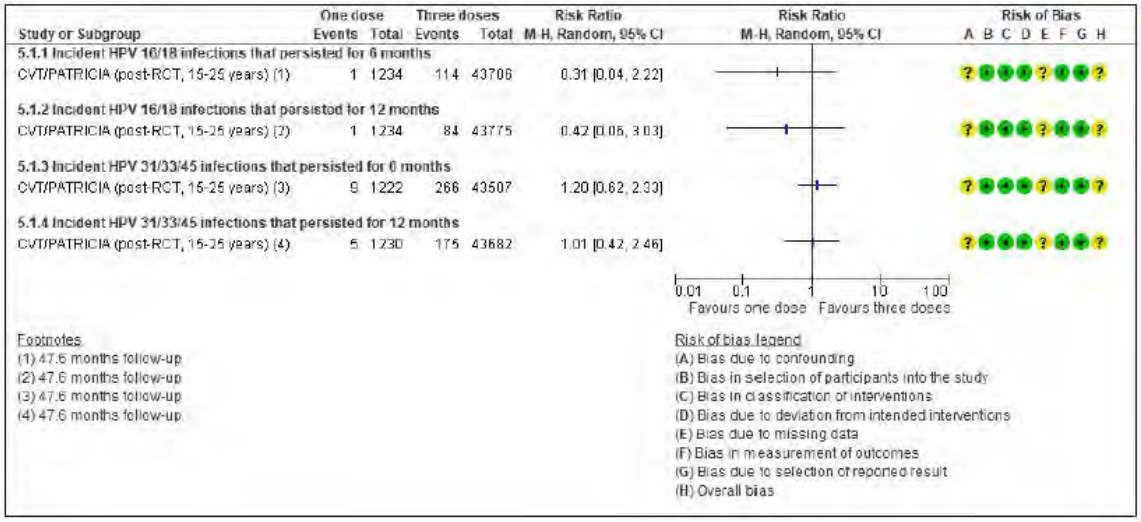


Figure 18: Persistent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 3 doses

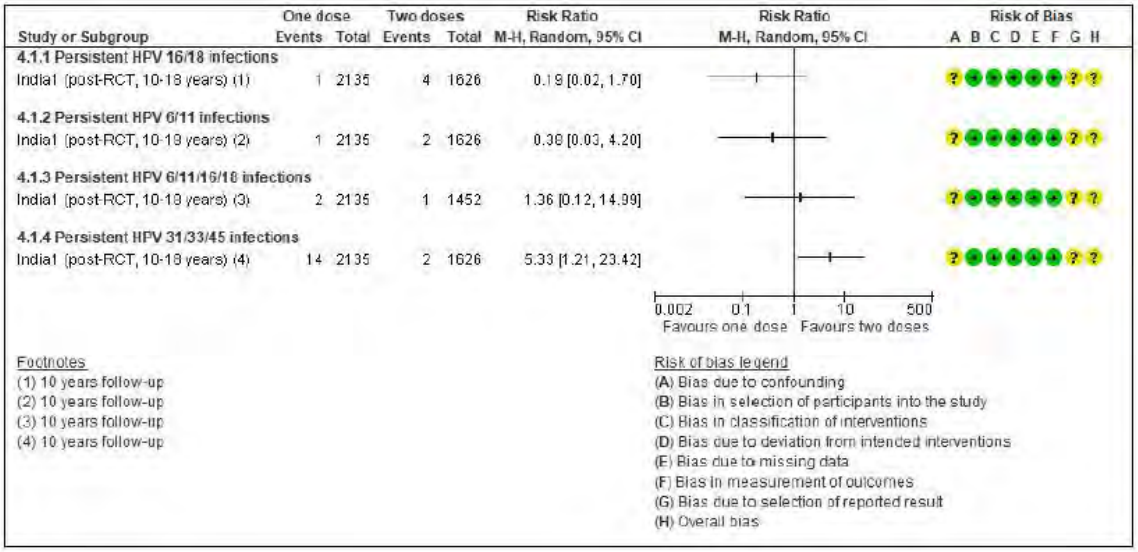


Figure 19: Persistent HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses 1 vs 2 doses

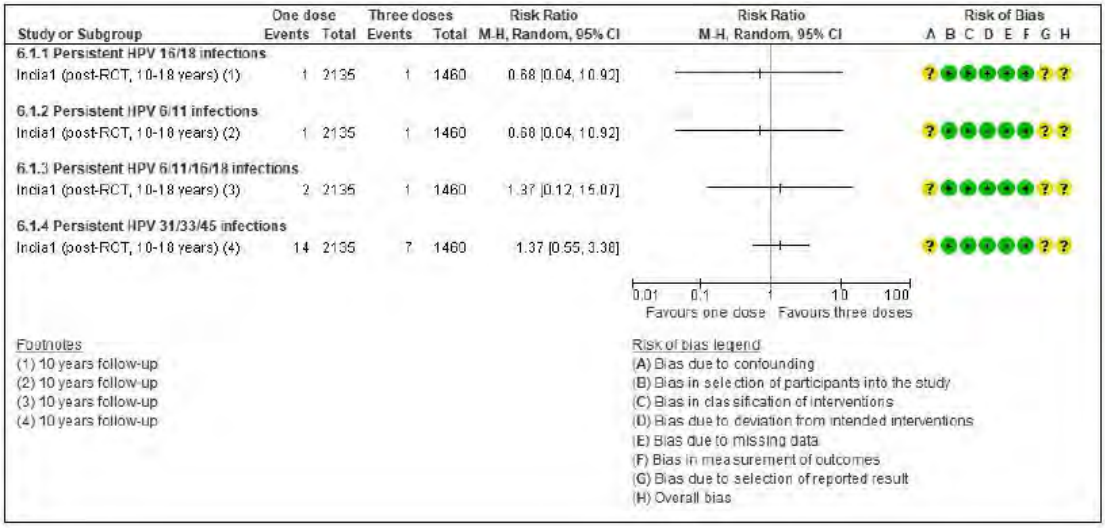


Figure 20: Persistent HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses 1 vs 3 doses

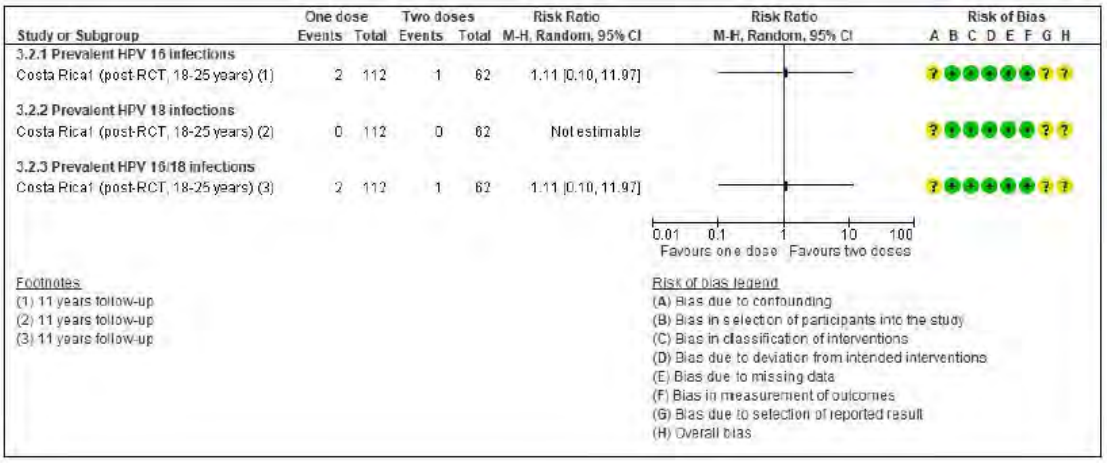


Figure 21: Prevalent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 2 doses

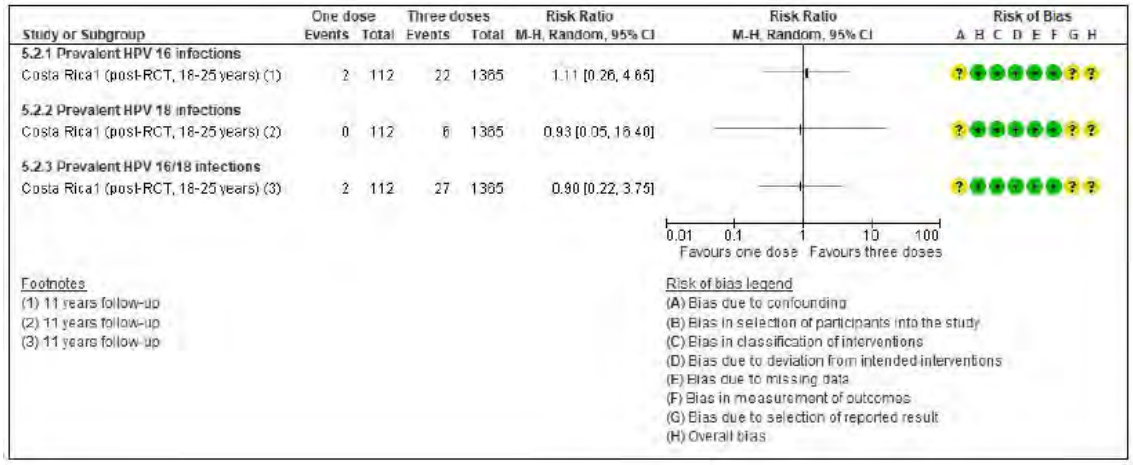


Figure 22: Prevalent HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 3 doses

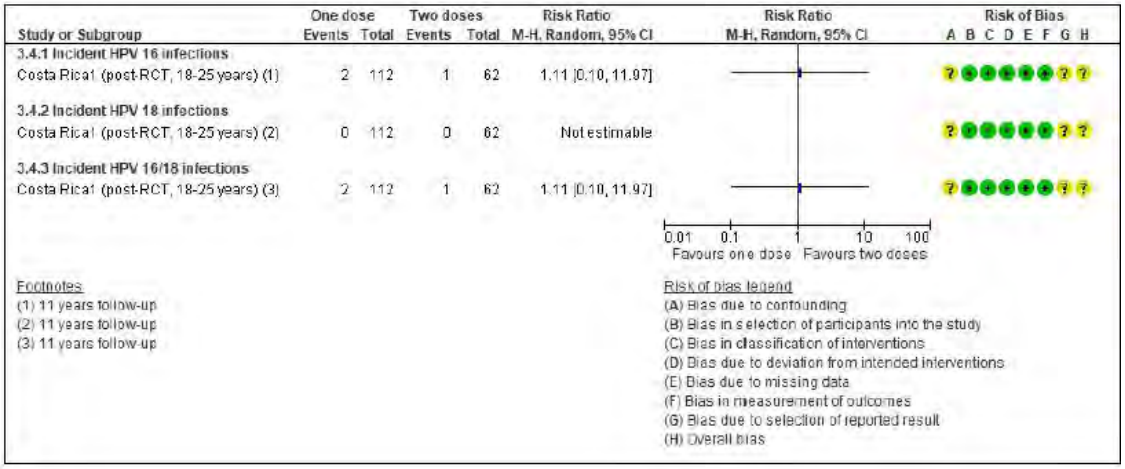


Figure 23: Incident HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 2 doses

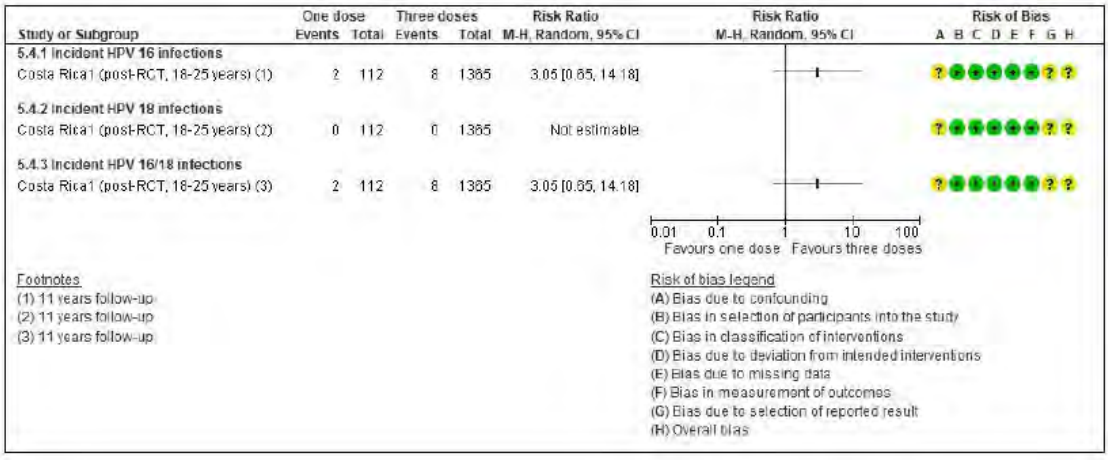


Figure 24: Incident HPV infections following bivalent vaccine (Cervarix) – post-hoc RCT analyses 1 vs 3 doses

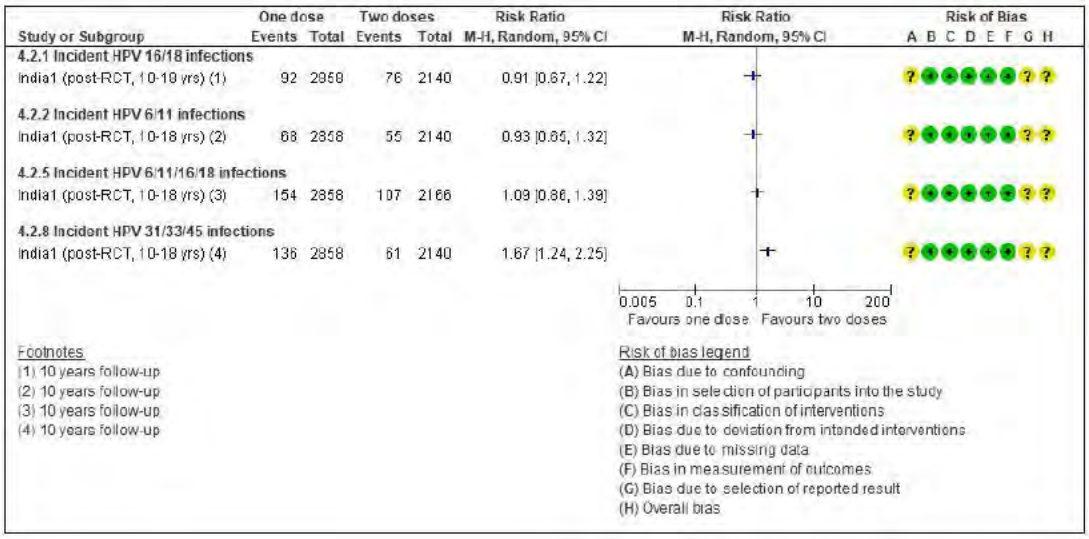


Figure 25: Incident HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses 1 vs 2 doses

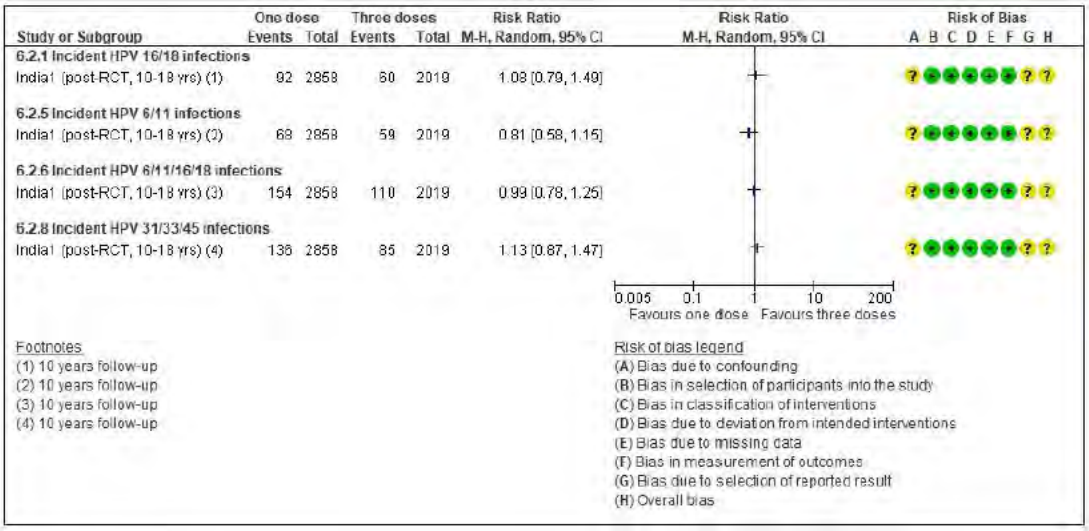


Figure 26: Incident HPV infections following quadrivalent vaccine (Gardasil) – post-hoc RCT analyses 1 vs 3 doses

Other clinical outcomes

- There was limited evidence to show a difference between one dose of HPV vaccine and two or three doses of HPV vaccine on genital warts, abnormal cytology, or CIN, with no RCT data available. The India IARC trial is as yet underpowered with no CIN2+ endpoints available.
- Thus the estimates of effect on clinical endpoints between one, two, and three doses of HPV vaccine come from observational studies that are at serious risk of bias due to confounding. These studies did not find a consistent significant effect in favour of two or three doses compared to one, although more studies of genital warts than cervical endpoints favoured three doses.

- Among the three observational studies that compared 2 or 3 doses to 1 dose for prevention of CIN *that adjusted for confounding*,[17,18,19] only one study detected a significant difference favouring 3 doses over 1.[19] (Table 4 and Table 5)

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI)
CIN2	Australia4	< 15 years	No buffer	HR 0.94 (0.73 to 1.21)
CIN2+	Denmark3	all ages	6 months	IRR 1.00 (0.61 to 1.64)
	USA21	12-26 years	24 months	OR 0.96 (0.55 to 1.68)
CIN3+	Denmark3	All ages	6 months	IRR 0.89 (0.53 to 1.52)
	Australia4	< 15 years	No buffer	RR 0.64 (0.35 to 1.16)

HR = hazard ratio; OR = odds ratio; IRR = incidence rate ratio; RR = risk ratio.

Table 4: Adjusted estimates of effect for CIN comparing one dose quadrivalent (Gardasil) vaccine with two doses

Outcome	Study	Age at vaccination	Buffer period	Adjusted estimate (95% CI)
CIN2	Australia4	< 15 years	No buffer	HR 0.91 (0.74 to 1.13)
CIN2+	Denmark3	all ages	6 months	IRR 0.99 (0.64 to 1.53)
	USA21	12-26 years	24 months	**OR 0.61 (0.38 to 0.99)**
CIN3+	Denmark3	All ages	6 months	**IRR 0.95 (0.60 to 1.51)**
	Australia4	< 15 years	No buffer	RR 0.66 (0.41 to 1.05)

* Estimates in bold indicate reduced risk of CIN after one dose. ** estimates indicate increased risk of CIN after one dose. HR = hazard ratio; OR = odds ratio; RR = relative risk.

Table 5: Adjusted estimates of effect for CIN comparing one dose quadrivalent (Gardasil) vaccine with three doses

The GRADE summary of evidence for one vs two doses is presented below.

[17] Brotherton JM, et al. Is one dose of human papillomavirus vaccine as effective as three?: A national cohort analysis. Papillomavirus Research. 2019:100177.
[18] Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: A Danish nationwide cohort study. Clin Infect Dis 2020 Feb 3;70(4):608-614. doi: 10.1093/cid/ciz239.
[19] Johnson Jones ML, et al. Effectiveness of 1, 2, and 3 doses of human papillomavirus vaccine against high-grade cervical lesions positive for human papillomavirus 16 or 18. American Journal of Epidemiology. 2020;189(4):265–276.

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[1]	not serious	not serious	serious[4]	none	2/3369 (0.06%)	8/4199 (0.19%)	**RR 0.32** (0.07 to 1.48)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕◯◯ Low	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% and following two doses 97% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% and following two doses 81.1% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.11 to 0.67 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1
Geometric mean titres (GMT) for HPV 18: follow-up 6 to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.17 to 1.07 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1

CI: confidence interval; **HPV:** human papillomavirus; **RCT:** randomized controlled trial; **RR:** risk ratio

1. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.
2. Downgraded one level due to imprecision, few events and a 95% confidence interval that encompasses a benefit, no effect, and a harm.

Table 6: GRADE evidence profile for single dose HPV vaccine compared with two doses of vaccine for HPV infection, seroconversion and antibody titres

7 Evidence reviewed: modelling the impact and efficiency of single dose schedules

The Working Group considered modelling prepared and presented by M Brisson, M Jit and K Prem. In the context of delayed introduction and delayed multi-age cohort catch ups (MACs) in many countries due to supply constraints and the COVID pandemic, HPV modellers were initially asked to consider whether a single dose MAC would be a good strategy for efficiency in the context of limited resources, both financially and in terms of vaccine supply availability. During the meeting, and in light of the Working Group interest in considering single dose for routine use, modelers were asked to present scenarios including data on single dose in routine programmes.

Goals considered were maximising of health benefits (population impact and absolute incidence reduction); in the context of limited supply, efficiency (how to best prevent cancers with available doses); and, in the context of budget constraints, cost effectiveness (what is maximum health benefit with minimum cost).

7.1 HPV ADVISE

The dynamic HPV ADVISE model[20] (Agent-based Dynamic model for VaccInation and Screening Evaluation), which includes 18 HPV types, was fitted to 4 LMICs (India, Vietnam, Nigeria, Uganda) to examine and compare population level impact and efficiency of various MAC strategies for different scenarios of girls only vaccination and different calendar years of vaccine introduction. The base case was a vaccination coverage of 80% with 9v vaccine (conclusions similar for 2v or 4v), assuming 2-dose VE 100% and 1-dose VE 85%, with 3 routine introduction scenarios for 9-year-olds starting in either 2018, 2020 or 2023, as well as routine 14-year-old vaccination starting in 2018. Starting routine introduction at any time after 2018 resulted in missed cohorts of girls with the goal of the MACs, whether 1 or 2 doses, being to try and reach the missed cohorts to achieve the same benefits as if vaccination was started in 2018.

The model prediction for Uganda found that if the country started with a 14-year-old program (vs age 9), a much greater reduction in cancer incidence would be achieved. A 14-year-old 2018 program with a 1 or 2 dose reverse MAC (i.e., catching up younger cohorts below the routine age of vaccination (9-13-year-old in this case) prior to shifting the routine age down to 9 years, rather than catching up older cohorts who missed out) in 2023 will achieve comparable cancer prevention benefits as a 1 dose MAC. It was noted that the MACs in the modelled scenario (which assumes one dose efficacy is lower than two dose efficacy) derive herd protection benefits from the 2 dose cohorts vaccinated ahead of and after them. The model produces similar findings for all 4 countries, as shown in Figure 27.

In a scenario assuming 1 dose has a 20-year duration of protection, compared to lifelong for 2 doses, the conclusion held: the reduction in cervical cancer incidence is similar with either a 1 or 2 dose MAC. The number of doses needed to prevent 1 case of cervical cancer through a MAC is a measure of vaccine efficiency. In all four countries, a 1 dose MAC was a more efficient strategy than a two dose MAC. Results for Uganda are shown in Figure 28.

[20] Brisson M, Laprise JF, Drolet M, et al. Comparative cost-effectiveness of the quadrivalent and bivalent human papillomavirus vaccines: a transmission-dynamic modeling study. Vaccine 2013; 31(37): 3863-71.

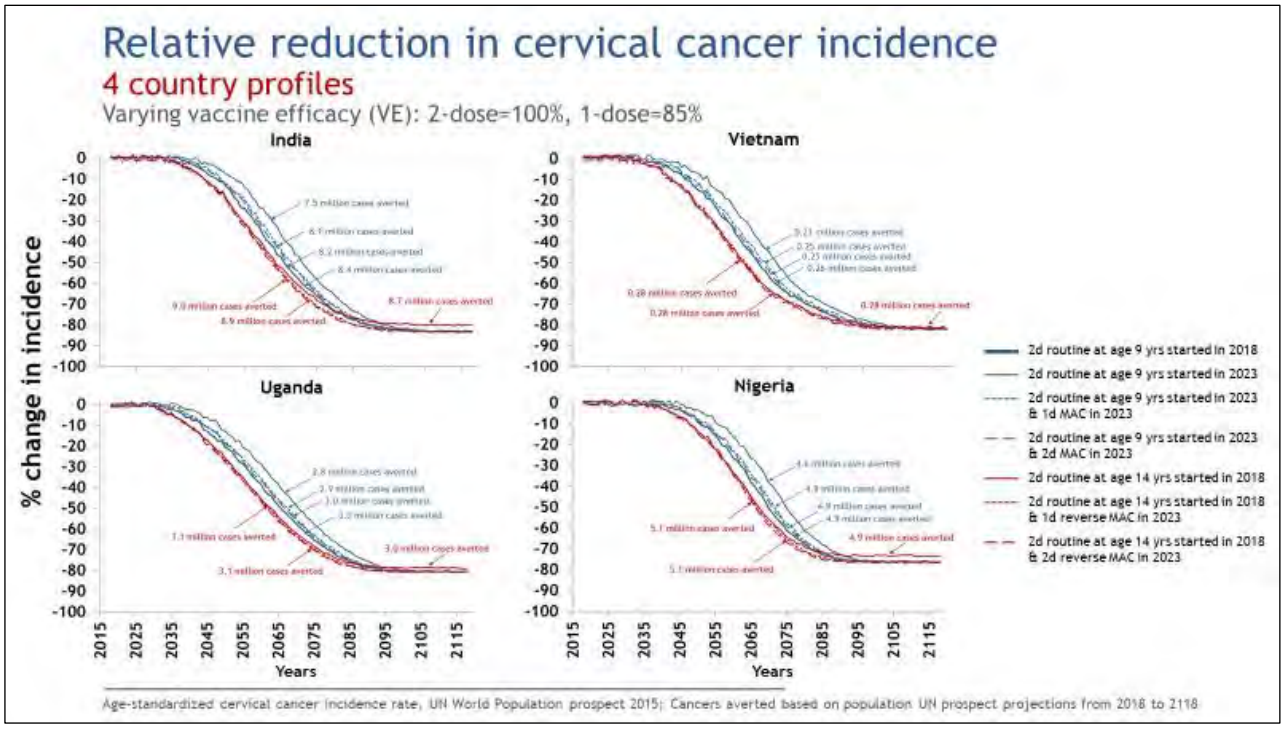


Figure 27: Overview of impact on cervical cancer incidence in 4 countries by vaccination strategy

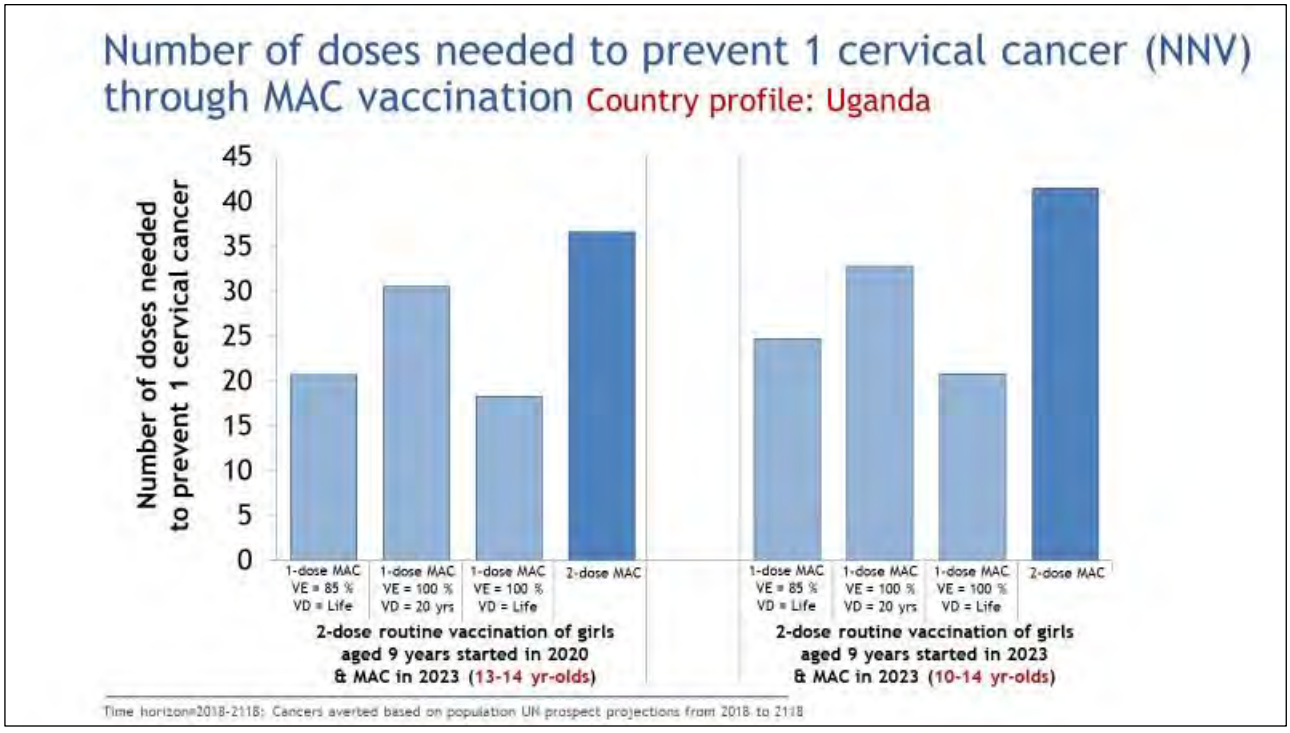


Figure 28: Number of doses needed to prevent one case of cervical cancer in Uganda: 1 vs 2 dose MAC

On request of the Working Group, the HPV ADVISE scenario for India of a one dose routine strategy and one dose routine plus MAC (85% VE) were presented, and both were compared with a 2-dose routine strategy at age 9. As shown in Figure 29, the analysis showed a steeper reduction in cervical cancer incidence with a 1 dose MAC than with a 2-dose routine program. But if 1 dose is eventually shown to have waning protection, the programme could switch to two doses: the model predicted that if one starts with a 1 dose MAC and a 1 dose routine programme and then switches later to a 2-dose programme, the approach would have still prevented more cancers than starting with a routine 2 dose strategy. This suggests that using a one-dose approach can be mitigated if required and that countries are still better off even if a second dose is ultimately needed. These data are also consistent with findings from the Harvard group model examining the same question.[21]

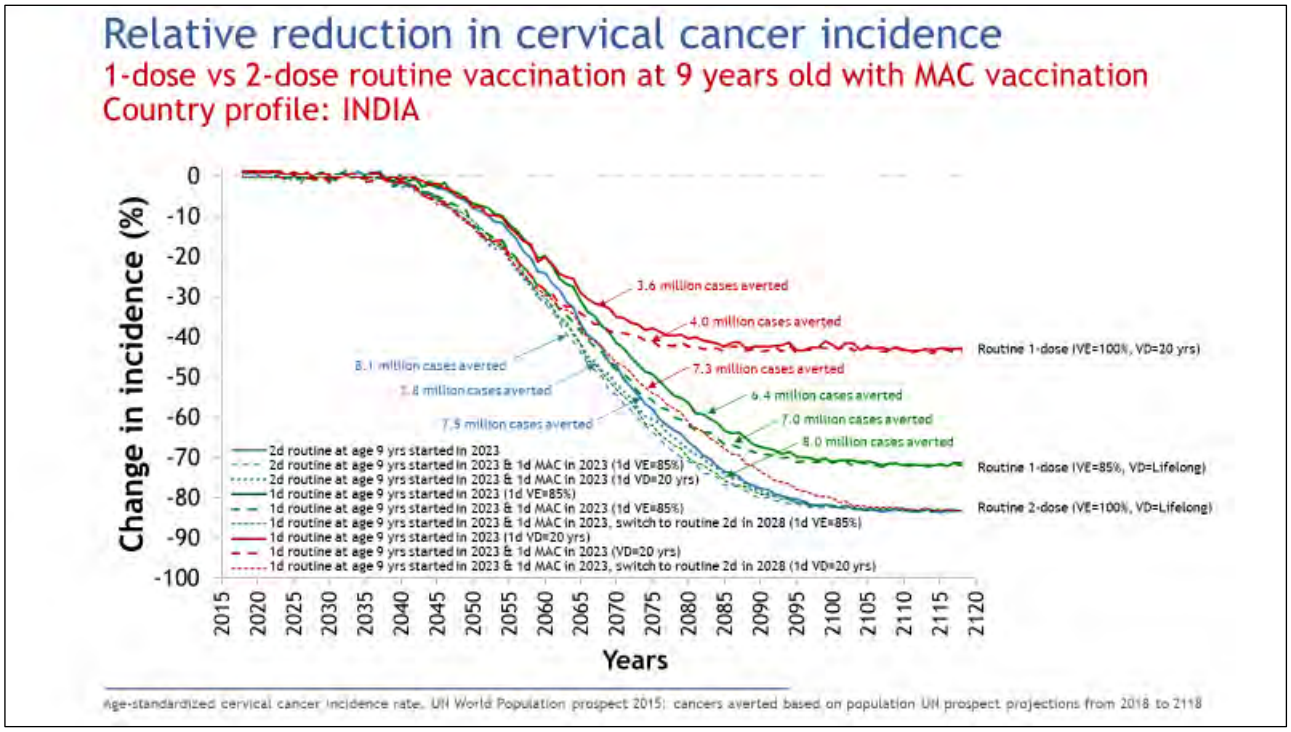


Figure 29: 1 dose and 2 dose HPV strategies in India: impact on cervical cancer incidence if 1 dose protection lasts 20 years and mitigation by reversion to 2 dose strategy

7.2 PRIME

The static PRIME model[22] (Papillomavirus Rapid Interface for Modelling and Economics) was used to evaluate vaccination strategies for the optimal allocation of HPV vaccines in the context of the available vaccine supply. The model assumed the use of a 2-valent HPV vaccine with a lifelong duration at 90% coverage and with a 1 dose VE of 85% and a 2 dose VE of 100%.

Routine vaccination of a single cohort minimised the time needed for all countries to introduce, with the fastest introduction possible with a one dose routine approach. However, MACs averted

[21] Burger Emily A, Laprise Jean-François, Sy Stephen, Regan Mary Caroline, Prem Kiesha, Jit Mark, Brisson Marc and Kim Jane J. Now or Later: Health Impacts of Delaying 1-Dose HPV Vaccine Implementation in a High-Burden Setting (January 31, 2022). Available at SSRN: https://ssrn.com/abstract=4022480 or http://dx.doi.org/10.2139/ssrn.4022480
[22] http://primetool.org/about-prime/

more deaths than the single cohort introduction approach. Introducing a routine 2 dose program alone would avert 4.1 million deaths, while adding a one-dose MAC averted 1.2 million additional deaths compared to 1.1 million for a 2 dose MAC (lower as a smaller total population can be covered when two doses are required). Introducing the routine vaccination of 14-year-olds and then switching later to the routine vaccination of 9-year-old girls once supply becomes available (reverse MAC) would prevent the most cancer deaths (an additional 2.6 million averted compared to a routine 2 dose 9-year-old program). (Figure 30)

However, if allocation is unoptimized (and a first year MAC cannot be guaranteed), then a routine 2 dose + 2 dose MAC strategy is very inefficient. Notably 2 doses with no MAC (the current default strategy) does not perform well compared to other strategies.

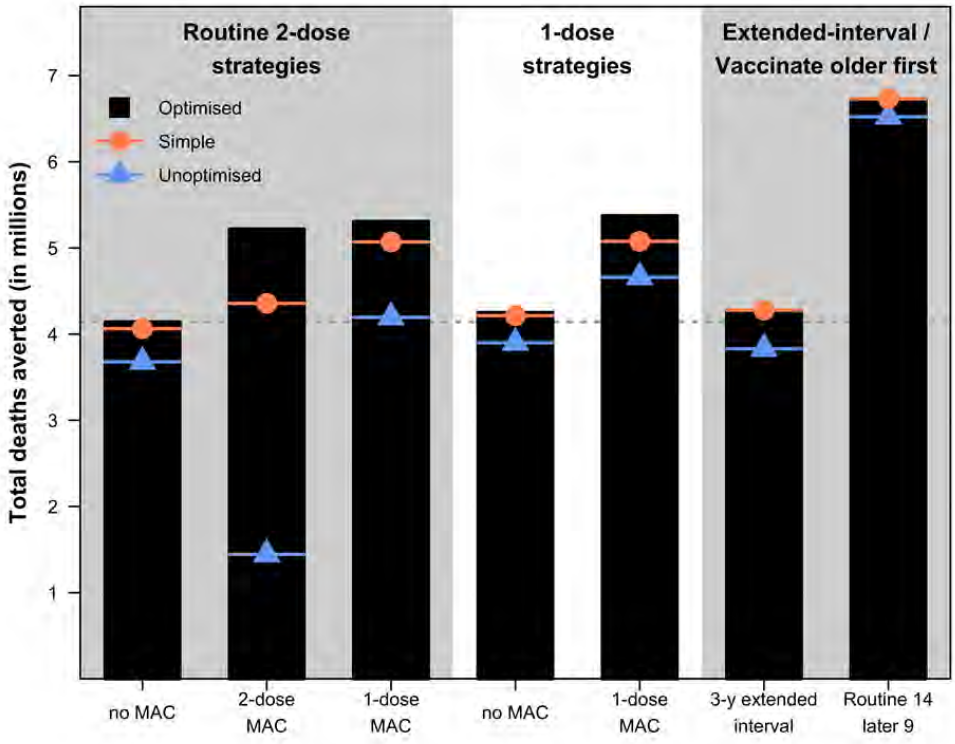


Figure 30: Cumulative deaths averted in vaccinated cohort in the setting of supply constraints: comparison of strategies and whether allocation of doses is optimised or not (PRIME)

7.3 Working Group Interpretation

The Working Group noted the conclusions of the modellers that there was consistency between the models, that MACs, particularly one dose MACs, were efficient and equitable, and the high human cost (>1M deaths) of a default two dose routine strategy and unoptimized vaccine allocations. The Working Group supported the modelled estimate of 85% VE for one dose as sufficiently conservative. The Working Group noted that in the HPV ADVISE model presented, any catch up MACs with more cohorts captured produced greater absolute benefits in the results presented than MACs with fewer cohorts included. They noted that this does NOT mean that catching up later with more cohorts is more effective than covering more cohorts prospectively initially and starting routine vaccination earlier. An additional benefit of MACs is the ability to catch up girls missed initially for programmatic reasons or because of COVID. The Working Group

noted that most efficient strategies in the modelling start with routine vaccination at 14 with a reverse MAC to 9-year-olds, but that this assumes high coverage can be obtained in 14-year-olds.

The Working Group discussed the potential complexity in communication and programmatic challenges for a programme simultaneously offering one dose to older girls in a MAC and two doses to younger girls in the routine programme. The Working Group noted that the modelling showed that giving a second dose is not efficient in a MAC as loss of effectiveness of 1 vs 2 doses is mitigated by herd protection. It was noted that the modelling did not look at vaccinating 15/16-year-olds as part of a MAC, despite one dose evidence currently being applicable to this group.

It was noted that the PRIME model allowed for routine programs to go back to giving routine cohorts 2 doses once supply constraints are resolved and only in sensitivity analysis kept one dose thereafter. Evidence should be more definitive by the time the supply issue is resolved as to whether the efficacy of one-dose is similar to that of the two-dose schedule or not.

The Working Group discussed the fact that the models do not take HIV into consideration and that there is currently no data to support removing the three-dose recommendation for girls living with HIV. It was noted however that status of girls is not known in some high-incidence countries nor is the impact of HIV seroconversion after vaccination on immune response. Implementing three doses in this group is programmatically challenging.

The Working Group agreed that the modelling emphasised the critical importance of offering vaccine to as many girls as possible before they age out.

8 Conclusions and recommendations

Please see Section 10 for the evidence to recommendations tables for the question

Should an off-label, permissive one-dose HPV vaccine schedule for use in routine and/or multi-age cohort (MAC) catch up strategies be recommended?

1. 0 vs a single dose of HPV vaccine
2. 1 vs two doses of HPV vaccine

8.1 What evidence gaps remain and what research is recommended to enable SAGE to make a universal one dose HPV schedule recommendation?

8.1.1 Immunogenicity and protection in HIV and immunocompromised populations

The view of the Working Group is that the most critical gap in research evidence currently relates to our understanding of the immunogenicity and protection provided by HPV vaccines in those living with HIV or other immune compromising conditions. This pertains to both multidose HPV vaccine courses and the response to one dose of vaccine. This is a critical issue because populations impacted by HIV have a high disease burden from cervical cancer. The Working Group noted the current difficulties, in areas such as South and Eastern Africa where HIV burden is high, in delivering the currently recommended two dose course and discussed at length the issues around delivering differential recommendations for girls living with HIV. The Working Group noted the lack of evidence as to whether previous vaccinated individuals maintain protection following HIV seroconversion. The Working Group notes that the HOPE study, an observational study of one dose in South Africa, will provide some data regarding immunogenicity and HPV prevalence among individuals who seroconvert to HIV after vaccination (see Appendix for outline of the HOPE study).

8.1.2 Kinetics of type specific antibody decline post vaccination

The Working Group noted the comparability of antibody levels between 9vHPV and 4vHPV vaccines, given the manufacturer's dosing changes to make them comparable, but also our lack of knowledge of the kinetics of individual additional 9vHPV types at the plateau phase and whether decay was different for different types.

8.1.3 RCT data comparing efficacy of one vs two doses and confirmation of duration of protection and efficacy in the longer term and impact on health outcomes (pre-cancers and invasive cancers)

The Working Group noted that, although the KEN SHE study provides strong high quality evidence to support one dose efficacy for 2vHPV and 9vHPV, and the India cohort study provides strong evidence supporting equivalence of one dose of 4vHPV to two or three doses, at this time there is no definitive RCT evidence establishing the equivalence of one dose of 2vHPV or 9vHPV with either the current two dose (prime boost at 0, 6-12m) or previous three dose (prime boost at 0,1-2, 6 m) schedules. As previously noted, the very high efficacy observed in KEN SHE for one dose efficacy against HPV16/18 infection (97%) makes it is implausible that future RCTs will identify an improved efficacy of multidose schedules over one dose. However, the Working Group notes that further RCT evidence will be advantageous to confirm the KEN SHE findings, extend them across available vaccines, confirm the robustness of protection over time and counteract

the potential uncertainties raised for policy makers by existing observational data (noting its inconsistencies and confounding but that the consistent impact of buffer periods suggests confounding by prevalent infection is important in interpretation of such data).

The Working Group notes that further RCT data will be available from the KEN SHE and DORIS trials and will be added to by data coming from the ESCUDDO trial (non-inferiority trial evaluating 1 vs 2 doses of 2v and 9v HPV vaccines among 12- to 16-year-old girls; computed vaccine efficacy (VE) against unvaccinated), PRISMA trial (1 vs 0 dose 2vHPV and 9vHPV vaccines among 18-30 year old women; vaccine efficacy against 16/18 infection) and HANDS trial (1 vs 2 doses of 9vHPV in 4-8 and 9-14 year olds compared to 3 doses in 15-26 year olds; immunobridging study to 36 months). Further follow up data will also come from the Costa Rica vaccine trial and from the non RCT studies PRIMAVERA (immunogenicity clinical trial one dose 2vHPV bridging to existing 3 dose 4vHPV efficacy data), HOPE (observational cohort of 1 and 2 dose 4vHPV), The Indian IARC study (4vHPV) and Thai one dose effectiveness study (2vHPV). These studies and expected timing of outcome data are detailed in Appendix section 9.4

The Working Group also noted that, although not a research need, clear guidance is required to ensure that manufacturers of emerging HPV vaccines and NITAGs can determine the evidence that would be required in order to use these emerging products in a one dose schedule. The Working Group recommends that such guidance should include a recommendation to immunobridge to plateau titres (from 24 months) rather than peak titres, measured using agreed standard and comparable immunoassays and against agreed benchmark titres established from efficacy studies.

8.1.4 Immunogenicity and protection in males

The Working Group noted the lack of evidence regarding one dose HPV vaccine immunogenicity and protection in males. Whilst equivalent immunogenicity and protection in males as females would be anticipated, research evidence is needed. Whilst the Working Group was not asked to explicitly reconsider the issue of vaccination of males as part of its deliberations, the Working Group noted that sex specific schedules may be impractical and challenging to communicate, that male vaccination may be a potentially useful strategy to support cervical cancer elimination in situations where female vaccination coverage cannot be further increased and that the vaccination of males provides primary protection to males against HPV and other HPV related diseases and cancers.

8.1.5 Immunogenicity and protection in older age groups

The Working Group noted the relative lack of evidence regarding one dose HPV vaccine immunogenicity and protection in those aged over 20 years at vaccination. Available data comes from the follow up of the Costa Rica Vaccine trial (age 18-25 at vaccination with 2vHPV, default one dose group n=112). Whilst sufficient immunogenicity and protection would be anticipated, given stable plateaus have been observed across age groups, research evidence is needed. A one dose schedule for all those who require catch up immunisation would be advantageous in terms of costs and logistics. The Working Group considers that further research could be of benefit to determine to what extent it could be of assistance in bringing forward elimination timelines once the supply constraints are resolved.

8.1.6 Implementation research to improve HPV vaccine coverage, including among HIV+ populations

The Working Group notes the large variations in coverage being achieved globally and supports the need for ongoing implementation research to support maximising coverage in all settings. Achieving high coverage in higher risk populations such as those living with HIV must be a global priority.

8.2 Should an off-label, permissive one-dose HPV vaccine schedule for use in multi-age cohort (MAC) catch up strategies be recommended?

The Working Group considered the evidence outlined above and concluded that the available efficacy, effectiveness and immunogenicity data fundamentally and strongly support the superiority of 1 HPV vaccine dose compared to zero doses for protection against oncogenic HPV infection. The available data are also consistent, although not conclusive at this time, with one dose and two/three doses being equivalent in effectiveness. As many girls are currently receiving zero doses at introduction of programmes due to supply constraints preventing MAC catch ups, and, given the modelling data supporting the impact and efficiency of one dose MACs compared to two, the Working Group concluded that a 1 dose schedule for MAC catch up should be recommended.

8.3 Should an off label, permissive one dose HPV vaccine schedule for use in the routine cohorts be recommended?

The Working Group considered that the available data and fundamental scientific principles of immunisation indicated that 1 dose should also apply to the younger routine cohorts, given the KEN SHE RCT data supporting high efficacy of one dose covers the age range 15-20 years at vaccination. Further, the Working Group considered that the available data and immunological principles also strongly support that the 3-dose schedule (0,1-2,6m) can be reduced to two doses (0,6-12m) in older ages and that a single dose can also be used up to the age of 20 years.

8.4 Recommendations

- To achieve the goals of the global strategy for cervical cancer elimination, SAGE recommends HPV vaccination for the primary target of 9-14-year-old girls, prior to sexual debut. National immunization programmes can use either a two-dose or a single-dose vaccination schedule.
- The option of a single-dose HPV vaccination schedule for routine and multi age cohort (MAC) catch-up vaccination in the primary target population is based on the very high vaccine efficacy of a single dose of HPV vaccine (97.5%) in girls up to 20 years of age observed in a high-quality RCT.
- This off-label option is recommended from a public health perspective because it provides comparable and high levels of individual protection, while being more efficient (fewer doses per cancer case prevented), easier to implement and less resource-intensive than a two-dose schedule. Modelling based on a single dose schedule predicts that the possibility of reaching a larger number of girls more rapidly and the resulting herd protection would compensate for any theoretical marginal difference in efficacy compared with two doses and has the potential to avert more cases of cervical cancer.
- A single-dose schedule can be considered for HPV vaccine products for which satisfactory efficacy and/or immunobridging data for a single-dose schedule are available. New and pipeline vaccines should generate evidence on peak and 24-month immunogenicity bridged to vaccines with proven single-dose efficacy.
- Since the single-dose efficacy data comes from a RCT and post RCT follow-up study involving girls up to age 20 years, either a two-dose or one-dose schedule can also be used for the vaccination of those who are 15-20 years old.
- For those older than 20 years, a reduced, two-dose schedule (instead of 3 doses previously) with a minimum interval of 6 months between doses can be used. Data on

immunogenicity and efficacy from a post RCT follow-up study gives confidence that this reduced-dose schedule will provide protection.

- It is uncertain whether immunocompromised individuals will be protected adequately by reduced dose schedules. Until further evidence is available, immunocompromised persons, irrespective of age, should be prioritized and should receive at least two doses but ideally three doses if programmatically feasible.
- SAGE recommends, as a priority, adequately powered trials with reduced dose schedules in immunocompromised individuals to generate evidence on the immunogenicity, efficacy and duration of protection, including on the serum antibody titre response in individuals who have received a single-dose HPV vaccine prior to HIV seroconversion.
- Additional evidence should also be generated on reduced-dose schedules in boys and older females and males, and implementation research carried out to improve HPV vaccine coverage.
- For global equity, and considering the improving supply situation, SAGE recommends all countries urgently introduce the HPV vaccine for the primary target of 9-14-year-old girls and, where feasible and affordable, to prioritize catching-up missed girls through multi-age cohort (MAC) vaccination. Introducing the vaccination of boys and older females should be postponed until the global supply situation is fully unconstrained.

Implementation consideration

- SAGE is deeply concerned about the stagnating pace of introductions, the low HPV vaccine coverage in many countries and the gap with the 2030 target of 90% coverage needed for elimination. The primary aim of the HPV vaccination programme should be to reach the highest level of population protection and vaccine coverage among girls before they reach 15 years of age with at least one dose of HPV vaccine, irrespective of the schedule. Multiple opportunities should be created to allow girls at any age before 15 years to receive at least one dose and to implement MAC vaccination catch-up to ensure the highest possible population protection.

9 Appendices

9.1 List of Participants (including Working Group membership)

SAGE members

- Professor Rakesh Aggarwal, Uttar Pradesh, India
- Professor Punnee Pitisuttithum, Bangkok, Thailand

Experts

- Professor Neerja Bhatla, New Delhi, India
- Dr Silvia Franceschi, Aviano, Italy
- Professor Eduardo Franco, Montreal, Canada
- Professor Suzanne Garland, Melbourne, Australia
- Dr Lauri Markowitz, Atlanta, USA
- Professor Andrew J. Pollard, Oxford, UK
- Professor Youlin Qiao, Chengdu, China
- Professor Helen Rees, Johannesburg, South Africa (former SAGE Member)
- Dr John Schiller, Bethesda, USA
- Professor Margaret Stanley, Cambridge, UK

WHO secretariat

- Paul Bloem
- Tracy Goodman
- Hiroki Akaba
- Joachim Hombach
- Christoff Steffen
- Tania Cernuschi
- Raymond Hutubessy
- Nathalie Broutet
- Shona Dalal
- Julia Brotherton (Consultant-rapporteur)

Regional Representative

- Phionah Atuhebwe, AFRO
- Lucia Helena de Oliveira, AMRO
- Kamal Fahmy, EMRO
- Liudmila Mosina, EURO
- Tondo Opute Emmanuel Njambe, SEARO
- Nyambat Batmunkh, WPRO

Invited experts

- Partha Basu, International Agency for Research on Cancer (IARC)
- Julia Lynch, International Vaccine Institute
- Deborah Watson Jones, London School of Hygiene and Tropical Medicine
- Ruanne V. Barnabas, University of Washington
- Sinead Delany-Moretlwe, University of the Witwatersrand
- Aimee R. Kreimer, National Cancer Institute
- Anne Schuind, PATH
- Marc Brisson, Université Laval
- Mark Jit, London School of Hygiene and Tropical Medicine
- Kiesha Prem, London School of Hygiene and Tropical Medicine
- Nicholas Henschke, Cochrane Response
- Hanna Bergman, Cochrane Response

9.2 Working Party Terms of Reference

Background

In 2018, the SAGE WG was established to review HPV vaccine policies and strategies to assess the contribution of HPV vaccination within the proposed Global Strategy Towards Elimination of Cervical Cancer. In 2019, the emerging global supply shortage of HPV vaccines led to a further request by SAGE for the WG to advise on alternative strategies to address the supply shortage and achieve more equitable global allocation of limited vaccine supply.

With this mandate, the SAGE WG reviewed systematic reviews and analysis of the available evidence with respect to HPV vaccine uptake and barriers to access; immunogenicity and efficacy of different schedules (single dose; two dose with different intervals); and vaccine demand and supply scenarios in the short and medium term.

SAGE concluded there was evidence to recommend a longer interval between doses, but insufficient evidence for single dose schedule or for a reduced 2-dose schedule for 15-18 year olds. Additionally, to prioritize available supply for the greatest impact on cervical cancer by vaccinating younger girls, SAGE recommended to temporarily pause vaccination of boys, older adults and multi-age cohort catch-up. SAGE also suggested alternative strategies to deal with the supply shortage including vaccinating girls at an older age (e.g., 14 years old) or use an extended interval of 3 or 5 years between doses.

In 2021, results from several studies, including two randomized control trials and an effectiveness study on single dose HPV vaccine schedules will become available, along with the ten year follow up data from the efficacy trial in India by IARC. The review of this data and recommendations towards schedule optimization would have important implications for the feasibility of reaching the 2030 target of the Global Strategy Towards the Elimination of Cervical Cancer of introducing HPV vaccine introduction in all countries and reaching 90% coverage.

Terms of Reference

To provide advice to SAGE on the use of vaccines against HPV in the context of advancing vaccination strategies towards the achievement of cervical cancer elimination the WG will:

• Review the evidence for optimization of HPV vaccination schedules;

• Discuss and propose additional research related to HPV vaccines and immunization to address evidence gaps.

Expected Outcomes:

- SAGE recommendation on the dosing schedule of HPV vaccines, including with regards to the possibility of single dose schedules and requirements for HIV-infected populations.
- Updated WHO position paper on HPV vaccines, including update of evidence on efficacy, effectiveness, impact and safety of all pre-qualified vaccine products and recommended schedules.

Beneficiaries of the updated policy guidance:

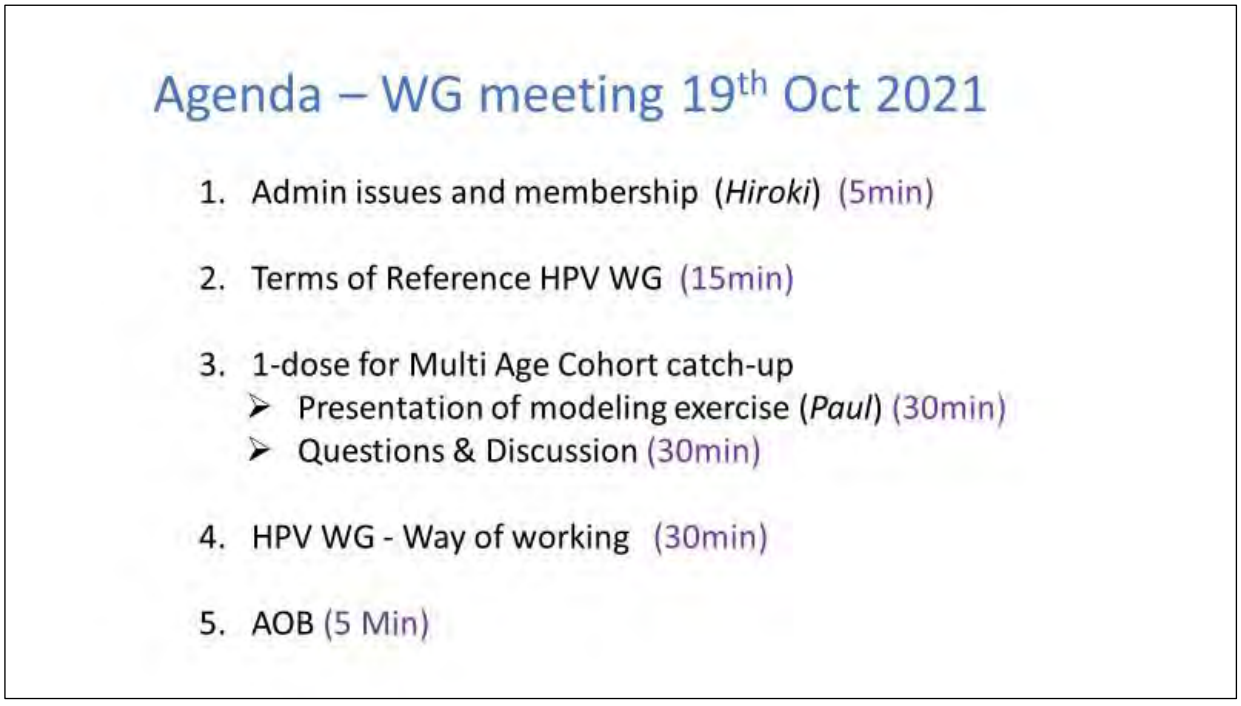
- EPI programmes in Member States allowing them to reach the targets for cervical cancer elimination in a more efficient way.
- NITAGs of LIC, MIC and HIC to facilitate making decisions on optimizing HPV vaccine schedules and ensure sustainability of HPV vaccination.
- Funding agencies such as GAVI supporting LMICs in HPV vaccine introduction.

9.3 Meeting agendas

9.3.1 Meeting 1: SAGE HPV Working Group Reconvening Meeting April 21,2021

Time	Topic	Presenters/ Participants
14.00 - 14.05	1. Welcome by Chair	Dr Rakesh Aggarwal
14.05 - 14.20	2. Briefing on single-dose HPV vaccination upcoming evidence from Clinical Trials *on behalf of the Single-dose HPV Vaccine Evaluation Consortium*	Aimée Kreimer, NIH Anne Schuind, PATH + WG
14.20 - 14.30	3. Questions and clarification	
14.30 - 14.55	4. Deliberations by WG Closed session	WG members
14.55 - 15.00	5. Next steps – Administrative announcements	Secretariat

9.3.2 Meeting 2: SAGE HPV Working Group October 19th, 2021



9.3.3 Meeting 3: SAGE HPV Working Group December 13-15th, 2021

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

20 AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

SAGE WORKING GROUP ON

HUMAN PAPILLOMAVIRUS IMMUNIZATION

13TH - 15TH DECEMBER 2021

DAILY 12.00-15.30

Venue Online

Agenda

Objectives

- To review ongoing and planned research as well as the available evidence on one-dose schedule;
- To identify potential gaps in evidence and additional research needs for a decision on a universal one dose recommendation;
- To discuss preliminary evidence towards a permissive one-dose recommendation for multi age cohort catch up vaccination.

Expected output

- Recommendations on evidence gaps and additional research needs for a decision on a universal one dose recommendation;
- Appraisal of available evidence for a decision on a permissive one-dose recommendation for multi age cohort catch up vaccination to maximize the public health benefit from available resources for HPV vaccination.
- Outline of Working Group background document , including preliminary conclusions and recommendations on research needed to inform a future universal one-dose recommendation.

Proposed questions to SAGE

1. Will currently planned and ongoing, purposefully designed one-dose HPV schedule studies and trials provide the evidence needed for SAGE to decide on a universal one dose recommendation? What evidence gaps exist and which research is recommended to fill these gaps?
2. Should an *off-label*, *permissive* one-dose HPV vaccine schedule for use in multi-age cohort (MAC) catch up strategies be recommended?

Note: A systematic review and meta-analysis of the available one-dose HPV vaccine schedule evidence will be done by Cochrane Response. Protocol will be available for review by end December 2021 and the preliminary results for discussion at a WG meeting in early 2022.

Tentative date for 2 day follow-up WG meeting: Week of January 31 or Feb 4, 2022

Day 1: Monday 13 December 2021

Chair: Rakesh Aggarwal

From 11.30	Log in Teams Session open	
12.00	**Opening Session**	
12:00–12:10	Welcome Consultation objectives and tasks, way of working Introduction of participants + Declaration of interests	R. Aggarwal
12:10–12:40	**Session 1: HPV vaccine uptake and barriers**	
	Question: What is the current status of HPV vaccine uptake and what are the main barriers to introduction, implementing MACs, including supply?	
12:10–12:30	• Update on HPV vaccine uptake (10') • Update on HPV vaccine supply situation (10')	P. Bloem T. Cernuschi
12:30-12:40	Questions for clarification	Plenary
12:40-15:00	**Session 2: One-dose research studies and evidence**	
	Questions: What data gaps are answered by the current research on one dose and what does current evidence show with respect to immunogenicity and efficacy of a single dose of HPV vaccine?	
12:40 -12:55	**IARC-India study** – 10 year follow up evidence	P. Basu
12:55 -13:10	Questions for clarification	Plenary
13:10 -13:25	**Thailand** effectiveness study	J Lynch
13:25 -13:40	Questions for clarification	Plenary
13:40 -13:50	***MINI Coffee, tea & exercise break***	
13:50 -14:05	**DORIS** immunogenicity bridging study (Tanzania)	D. Watson
14:05 -14:20	Questions for clarification	Plenary
14:20 -14:35	**Kenshe** study (Kenya)	R. Barnabas
14:35 -14:50	Questions for clarification	Plenary
14:50 -15:00	***Summary of Day 1 and Closure***	***R. Aggarwal***

Day 2: Tuesday 14 December 2021

From 11:30	Log in – **ZOOM** session Open	
Chair: Rakesh Aggarwal		
12:00–13:40	**Session 3: Research on alternative schedules for new and pipeline vaccines** **Closed Session**	
	Questions: What research are (pipeline) producers conducting or planning on the efficacy & immunogenicity of alternative (one dose) schedules and what are the implications of a potential 1-dose licensure of HPV vaccines?	
12:00–12:15	**Innovax** Cecolin vaccine and 9 valent pipeline vaccine	
12:15–12:23	Questions for clarification	Plenary

12:25–12:40	**Walvax**, 2-valent pipeline vaccine (Licensure submitted)	
12:40–12:48	Questions for clarification	Plenary

12:50–13:05	**CNBG**, 4-valent vaccine pipeline vaccine (Phase III)	
13:05–13:13	Questions for clarification	Plenary
13:15–13:30	**Serum Institute of India**, 4-valent pipeline vaccine (Phase III)	
13:30–13:40	Questions for clarification	Plenary
13:40–13:50	***MINI Coffee, tea & exercise break***	
	Continuation on Teams session	
13:50-15:20	**Session 4: Evidence to be generated by planned one-dose research studies**	
	Question: What trials and studies are planned to generate evidence in the coming years and what gaps in the evidence can be addressed through additional research?	
13:50–14:05	**HOPE** study (South Africa) incl HIV+ (results in early 2022)	S. Delany-Moretlwe
14:05–14:25	**CVT**, **ESCUDDO**, **Primavera** and trials	A. Kramer
14:25–14:40	**Hands** trial **PATH** One dose Trial with **Cecolin** (planned)	A.Schuind
14:40–14:55	Questions for clarification	Plenary
14:55-15:00	***Summary of Day 2 and Closure***	**Rakesh Aggarwal**

Day 3: Wednesday 15 December 2021

11.30	Log in – Teams session Open **Chair: Rakesh Aggarwal**	
12:00-13:00	**Session 5: Modelling to support one-dose in MAC recommendation**	
	Question: Does modelling support a recommendation on one dose for MAC populations? What critical factors do sensitivity analyses identify? Is this an effective use of available resources/supply (allocative efficiency)?	
12:00–12:30	Combined presentation by HPV Modelers on 1 dose for MAC impact	M. Brisson K. Prem, M Jit
12:30–12:50	Discussion and questions for clarification	Plenary
12:50–15:15	**Final session: Preliminary recommendations & SAGE background document** **CLOSED SESSION**	
12:50–13:30	Discussion to develop preliminary conclusions and recommendations • Evidence and research gaps for decision on universal 1 dose recommendation • Evidence for a permissive 1-dose recommendation for MACs	SAGE WG Members
13:30–13:40	***MINI Coffee, tea & exercise break***	
13:40–14:30	Continued	SAGE WG Members
14:30–15:20	Discuss next steps: • HPV systematic review, WG review of protocol • Agenda for Jan/Feb 2022 meeting • Guidance on content & structure of WG background document for SAGE, GRADEing Tables Identifying Next steps	
15:20	**Closure of meeting**	**Rakesh Aggarwal**

9.3.4 Meeting 4: SAGE HPV Working Group February 8-9th, 2022

Immunization, Vaccines and Biologicals (IVB)
World Health Organization

20 AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

SAGE WORKING GROUP ON

HUMAN PAPILLOMAVIRUS IMMUNIZATION

8TH - 9TH FEBRUARY 2021

DAILY 12.00-15.30

Venue Online

Agenda

Objectives of the WG

- To review ongoing and planned research as well as the available evidence on one-dose schedule;
- To identify potential gaps in evidence and additional research needs for a decision on a universal one dose recommendation;
- To discuss preliminary evidence towards a permissive one-dose recommendation for multi age cohort catch up vaccination.

Expected output

- Recommendations on evidence gaps and additional research needs for a decision on a universal one dose recommendation;
- Appraisal of available evidence for a decision on a permissive one-dose recommendation for multi age cohort catch up vaccination to maximize the public health benefit from available resources for HPV vaccination.
- Outline of Working Group background document , including preliminary conclusions and recommendations on research needed to inform a future universal one-dose recommendation.

Proposed questions to SAGE

1. Will currently planned and ongoing, purposefully designed one-dose HPV schedule studies and trials provide the evidence needed for SAGE to decide on a universal one dose recommendation? What evidence gaps exist and which research is recommended to fill these gaps?
2. Should an *off-label*, *permissive* one-dose HPV vaccine schedule for use in multi-age cohort (MAC) catch up strategies be recommended?

Expected outputs of Feb 8-9 Meeting

- Review preliminary findings of the systematic review of HPV vaccines (comparisons 0 vs 1 dose and 1 vs 2 (or 3) doses);
- Formulate draft recommendations including research priorities to SAGE and develop supporting *evidence to recommendation tables*.
- Identify roadmap for WG to prepare report and present at SAGE April meeting

Day 1: Tuesday 8 February 2022

Chair: Rakesh Aggarwal

From 11:30	Log in – Teams session Open	
12:00–12:15	Meeting objectives and tasks Review of outcomes Dec 2021 meeting	R. Aggarwal
12:15–13:45	**Session 1: HPV vaccine systematic review findings** *Question: What is the consolidated evidence from an updated systematic review on the immunogenicity and effectiveness of a single dose compared to zero, two (or three) doses of HPV vaccine?*	
12:15–13:00	Preliminary findings *phase 1* Cochrane Review systematic review on HPV vaccines (0 vs 1; 1 vs 2/3), overview of phase 2 (additional analyses, comparisons & populations)	N. Henschke
13:00-13:45	Discussion and identification of actions towards finalization systematic review	Plenary
13:45 -14:00	***MINI Coffee, tea & exercise break***	
14:00-15:00	**Session 2: Draft recommendations for SAGE report (closed)**	
14:00 -15:00	Discussion to preliminary conclusions and draft recommendations • Evidence for a permissive 1-dose recommendation for MACs • Evidence for a permissive 1-dose recommendation for routine • Research gaps for decision on universal 1-dose recommendation	Plenary
15:00 -15:10	***Summary of Day 1 and Closure***	***R. Aggarwal***

Day 2: Wednesday 9 February 2022

From 11:30	Log in – Teams session Open	
Chair: Rakesh Aggarwal		
12:00–14:30	**Session 3: Recommendations and Evidence to Recommendation tables** **Closed Session**	
	Questions: what are the draft recommendation to SAGE and what considerations have been taken into account in developing the draft recommendations	
12:00–12.10	Overview of Evidence to Recommendation tables	WHO
12.10-13:40	Review Evidence2recomemdnation Table 0 vs 1 comparison	Plenary
	Review Evidence2recomemdnation Table 1 vs 2 comparison	
13:30–13:40	***MINI Coffee, tea & exercise break***	
13:40–14:30	Continued	
14:30-15:00	**Session 4: Next steps: roadmap to the April SAGE meeting generated by planned one-dose research studies**	
	Question: What are planned and proposed steps to finalize the report to SAGE and to plan the HPV discussion at SAGE ?	
14:30–14:55	**Next steps overview of process and timelines** • Validate next steps and timelines • Agree on process and timelines for finalizing WG report to SAGE • Session and presentations to SAGE April 7 meeting	Plenary
14:55-15:00	***Summary of meeting and Closure***	**Rakesh Aggarwal**

9.4 One dose trial data to come: study outlines and expected data

9.4.1 Summary of further data to come from reported studies (India IARC/KEN SHE/DoRIS)

As summarised in Figure 8 (Section 5 above), further results from KEN SHE reporting durability of 1 dose efficacy are expected in Q4 2023. Participants will receive blinded cross-over vaccination, ensuring all receive HPV vaccination, with an additional 18 months follow-up to evaluate single-dose durability. The study will also look at those who seroconverted to HIV post vaccination.

Further data from the IARC India study are expected in mid 2023 reporting persistent infection data from over 3500 one dose recipients and the CIN2+ endpoint from over 1500 one dose recipients. In 2025 persistent infection data will be available from over 4000 one dose recipients and in 2026 CIN2+ data from over 3500 screening one dose recipients.

Further results from DoRIS are pending with results for month 36 analyses underway, and M60 visits commencing in March 2022, as well as immunobridging to KEN SHE.

9.4.2 Overview of design and data to come from HOPE

The HOPE study is assessing the impact of 1-dose catch up in South Africa, which introduced routine 2 dose 2vHPV in 2014 in a school-based program for 9-year-olds. Impact is being assessed using repeated cross-sectional surveys of HPV16/18 prevalence in girls 17-18 years attending PHC services (in 4 provinces in sentinel clinics). One-dose vaccine was given in 2019 in a single district in Free State to a target population of 6700 girls in grade 10 (around 15-16 years old) in 66 high schools, achieving 72% coverage of eligible girls. HPV prevalence at sentinel clinics is measured using a self-collected swab, with a tablet based self-interview collecting behaviour and vaccination history. HIV testing and clinical data are extracted. Vaccination status is ascertained through a study-specific register and access to the Department of Health register. A nested sub-study of 400-450 vaccinated 17–18-year-olds will measure antibodies at 24 and 48 months by HIV status and avidity and neutralising ability by HIV status and recency of HIV infection. Recency of HIV acquisition will be assessed using recency assay testing at the National Institute.

In preliminary results, the 2019 baseline survey found an HPV16/18 prevalence of 31% in HIV-positive women and 18% in HIV-negative women. Prevalence was associated with number of partners. Survey 2 in the one dose eligible cohort is in progress.

Results are expected end-February 2022 for the main outcome of HPV prevalence in one dose vaccinated vs non-eligible, noting that the HIV status sub-study will take longer. Final study results are expected late 2024.

9.4.3 The Original Costa Rica 2vHPV trial of 18–25-year-olds

At 10-years for the HPV16/18 prevalent infection endpoint, 3 doses had 80% efficacy and this was similar for 1 dose. Cross protection was also observed. Antibody findings show stable HPV16 serum antibodies that are 4-fold lower for 1 dose than with 3 doses, but levels are stable. An in-press paper (Tsang S et al.) shows HPV16 avidity is lower in the 1 than 3 dose group but with no degradation of one dose avidity over time. Final immunogenicity analyses will be run at 20 years (16 years data in 2022).

9.4.4 Overview of design and data to come from ESCUDDO

This is a randomised non-inferiority trial of 1 vs 2 doses of 2v and 9v in 20,300 12-16-year-old girls against incident persistent cervical infections with 5 years follow up. A second coprimary endpoint is to assess one dose vs zero doses through a survey of 17-20-year-olds for the zero dose group. A concern has been raised however that pre and post assessments may not be valid if the COVID pandemic alters acquisition so a post-covid end of study survey of 16.5-21.5-year-olds is planned in addition (n=3000). Preliminary results will be presented late 2023/early 2024 with final study analysis in late 2025.

9.4.5 Overview of design and data to come from Primavera

Primavera is an immunobridging study comparing HPV16/18 antibody levels in 620 girls 9-14 years after 1 dose of 2vHPV with levels achieved in 620 women 18-25 years who receive 3 doses of 4vHPV. It is a non-randomised open label bridging trial, using a lower bound ratio of GMT >0.67. Serology collection will occur at months 12/24/36. M24 interim analysis will be available at the end of 2022 and final analysis in 2024.

9.4.6 Overview of design and data to come from PRISMA

PRISMA is a RCT of 1 dose 2vHPV and 9vHPV vaccination in >5000 adult women aged 18-30 years. The study aims to provide data to potentially extend catch-up recommendations to age 30 once there is an excess of HPV vaccines to accelerate global cervical cancer elimination by use of a one-time mass catch-up. The study will assess one dose HPV (2vHPV or 9vHPV) compared to dTpa in three arms against the endpoint of incident cervical infection with HPV16/18. Study launch is Q1 2022, with 36 months of follow up against virological and immunological endpoints and data expected to be ready by 2027.

9.4.7 Overview of design and data to come from HANDS

The HANDS trial is investigating the safety and immunogenicity of a 9vHPV vaccine in young children 4-8 years of age in order to be able to extend the age indication to facilitate school vaccination (Sponsor MRC Unit Gambia and LSHTM, PI Ed Clarke). 9vHPV in 15–26-year-old females 3 doses (reference) is compared to 9vHPV in 9-14-year-old and 4-8 year olds randomised to 1 or 2 dose schedules measuring immunopersistence to 36 months. 1-dose cohorts will receive a second dose at the end of study. The last subject was recruited in June 2021 with 24-month data expected in 2023 and the study is due to complete follow up in mid-2024.

9.4.8 Overview of design and data to come from the Thailand effectiveness study

This observational cohort study is comparing vaccine effectiveness against prevalent HPV16/18 infection of one versus two doses of 2vHPV given in a school-based program to Grade 8 girls (age <15 years) in two similar Thai provinces. Udon Thani (Single Dose) and Buriram (Two-dose). HPV prevalence is assessed amongst a cross sectional sample of 2600 students per province (irrespective of vaccination status) through urine sampling (collected with the Colli-Pee device and tested using Cobas 4800 HPV test with Cobas positive typed using Anyplex). Urine samples were collected at baseline from Grade 10 students, taken in 2018/2019 at the time of vaccination of the Grade 8 cohort, with repeat collection at two and four years later (in Grade 10 and 12 from the vaccinated cohort and Grade 12 in the unvaccinated cohort). Sexual behaviour is assessed using a self-administered survey and a subset (n=200 per province) undergo serology studies. Analysis is at the cohort level with vaccinated and unvaccinated participants identified

through linkage to health department records through a unique ID. Publication of year 2 data is pending, with final year 4 follow up data expected in 2023.

9.4.9 Overview of design and data to come from CHOISE

The CHOISE study is an open label RCT comparing HPV vaccine options in an immunogenicity and safety evaluation (PATH study sponsor – Bangladesh and Ghana study sites). 9-14-year-old girls were recruited into 5 study groups N=1025 (205/group):2 dose Cecolin 0,6/0,12/0,24m compared to 4vHPV vaccine 0,6 m, and with a mixed schedule arm 4vHPV day 1, Cecolin 24m. The rationale of the 25-month study is to generate additional data on Cecolin for global policy and country adoption by establishing non- inferiority of 2 dose Cecolin vs 4vHPV. Further considerations are to bridge to one dose efficacy studies and persistence to 24 months after one dose. The study had fully recruited in Nov 2021 with results expected in 2024.

10 Evidence to recommendations tables

The tables assessing 0 vs 1 dose commence on page 53.

The tables assessing 1 vs 2 doses commence on page 65.

World Health Organization

Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[23]

Question: Should an *off-label*[24], *permissive* one-dose HPV vaccine schedule for use in routine and/or multi-age cohort (MAC) catch up strategies be recommended?

Population: Main population is pre-adolescent and adolescent girls (9-14 years old), but boys and older adults are also included.
Intervention: Single dose vaccination; bivalent (Cervarix and Cecolin), quadrivalent (Gardasil), and nonavalent vaccines (Gardasil 9).
Comparison(s): No vaccination
Outcome:
Clinical outcomes: including, but not limited to invasive cervical, vaginal, vulval, anal, penile or head and neck cancer; cervical intraepithelial neoplasia (CIN) grade 3+; CIN2+; histological and cytological abnormalities; anogenital warts; high risk HPV infection (genotype-specific prevalence, incidence and/or persistence)
Immunological outcome; seroconversion or seropositivity; geometric mean titers (GMT) of HPV antibodies

Background: As of March 2022, 117 countries introduced HPV vaccine in their national immunization schedules, but these countries represent only a third of the global population of girls and 40% of the global burden of cervical cancer.

In October 2019, SAGE reviewed the evidence on a single dose of HPV vaccines to protect 9-14-year-old girls, the primary target population, against cervical cancer. SAGE concluded the quality and amount of evidence was insufficient for this policy decision and

[23] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[24] *The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.*

that the evidence from the purposefully designed single dose randomized control trials (RCTs) was required to inform policy decisions. Several of the RCTs and effectiveness studies designed to assess single dose schedules have generated interim results during 2021.

In November 2020, the World Health Assembly adopted the Global Strategy towards the elimination of cervical cancer. The strategy calls on each country to introduce HPV vaccination by 2030 and set a target of 90% of girls fully vaccinated with HPV vaccine by age of 15. HPV vaccine coverages are below the target of 90% in the majority of countries and the observed high drop out between the first and the second dose indicate programmatic challenges.

Programmatic challenges to introducing the vaccine include high cost and supply constraints. The latter have affected in particular Low-and Middle-income countries since 2018 and led to delayed introductions and delayed or canceled multi age cohort catch up strategies in GAVI eligible countries.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	HPV infection with oncogenic HPV types causes an estimated 604,000 cases of cervical cancer worldwide (Globocan, 2020). HPV infection also causes a proportion of cancers of the anus, the oropharynx, the vulva and vagina, and of the penis. Of HPV-associated cancers, HPV types 16 and 18 are associated with 85% of HPV-related head and neck cancers and 87% of anal cancers – the second and third most frequent HPV-related cancers with, respectively, 38 000 and 35 000 estimated cases per year. Martel et al., Int. J. Cancer: 141, 664–670 (2017) VC 2017 Anogenital HPV infection can result in benign skin and mucosal tumors, including anogenital warts in men and women The estimated median annual incidence of new anogenital	
		☐	☐	☒	☐		

World Health Organization

					warts was 137 per 100 000 men and 121 per 100 000 women. (Patel H et al. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases, 2013;13:39)	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Recent data shows that single dose HPV vaccine is effective for both clinical and immunological outcomes. See the summary table of Systematic Review by Cochrane Group. (see the Cochrane Systematic Review). In particular, there is one high quality RCT study which shows high Vaccine Efficacy (>95%) of single dose HPV vaccine in adolescent girls/ young women 15 to 20 years old. Modeling suggests that under an elimination scenario (all countries introduce by 2030 and all countries include a first year multi age cohort catch up for 10-14-year-old girls), this can avert at least 1.2 million additional cases of cervical cancer compared to only vaccinating a routine cohort of girls (Prem& Jitt, 2021)	
	Harms of the intervention Are the undesirable	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Since licensure in 2006, over 500 million doses of HPV vaccines have been distributed. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses. No other serious adverse reactions have been identified and HPV vaccines have an excellent safety profile (GACVS 2017).	

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	anticipated effects small?			
	Balance between benefits and harms	*Favours inter-vention*: ☒ *Favours com-parison*: ☐ *Favours both*: ☐ *Favours neither*: ☐ Unclear: ▱	The benefits of protection against any HPV related diseases, cervical but also other forms of cancers and genital warts, overweigh any adverse effect of vaccination (e.g., pain during vaccination, AEFIs)	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies*: ☐ *Very low*: ☐ *Low*: ☐ *Mod-erate*: ☒ *High*: ☒ Safety of the intervention *No included studies*: ☐ *Very low*: ☐ *Low*: ☐ *Mod-erate*: ☐ *High*: ☒	See related GRADE tables in the Cochrane review. The safety of HPV vaccine has been confirmed by GACVS and informed by data from large, high quality datasets from post surveillance systems (see the GACVS Report). https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety	Two boxes have been ticked: The high quality refers to a RCT that provided shorter term efficacy data. The moderate quality refers to a post RCT follow up study on long term efficacy.
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability*: ▱ *Possibly important uncertainty or variability*: ▱ *Probably no important uncertainty or variability*: ☒ *No important uncertainty or variability*: ▱ *No known undesirable outcomes*: ▱	While global representative data are missing, there is no important uncertainty around the relative weight that the target population attributes to the desirable outcomes (i.e., protection conferred by the vaccine) and the undesirable outcomes (i.e., the currently reported AEFIs). There is no uncertainty about the value placed on prevention of cervical cancer and high acceptance of the vaccines indicated by high coverage (>80%) achieved in many programs attest to that (Bruni et al, 2021)	

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	The target population assigns more weight to the desirable effects than to the undesirable effects. Large benefits can be obtained relatively to potential undesirable effects. Effectiveness data have shown that taking the vaccine can reduce the chance to get cervical cancer by 88% (Lei J et al. NEJM 2020). Minor AEFIs (e.g. pain) are reported; the risk of serious events like anaphylaxis is very rare; no other serious adverse events have been identified.	
RESOURCE USE	Are the resources required small?	*No* ☒		*Uncertain* ☐	*Yes* ☐		*Varies* ☐	HPV vaccine is relatively more costly than other childhood vaccines. In addition, vaccine delivery costs have been demonstrated to be high for HPV vaccines (Jit. M, 2021 https://doi.org/10.1016/j.jval.2020.07.012.) From the immunization programme perspective, additional resources are needed, including financial costs and human resources, to introduce HPV vaccine to the primary target adolescent girls.	
		No		*Uncertain*	*Yes*		*Varies*		

	Cost-effectiveness	☐	☐	☒	☐	Previous studies have shown that HPV vaccine is a cost-effective intervention in various country settings. (Abbas et al. 2020 https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30022-X/fulltext) While no CEA for LMICs was done for single dose schedules, similar gains will be obtained with lower costs, and therefore single dose schedule HPV vaccination will be a more cost effectiveness intervention (than with 2 doses).	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	It is important to protect girls against HPV infection, especially in low- and middle-income countries where approximately 90% of cervical cancer cases occur and secondary prevention through screening is often inaccessible and of low quality. In addition, currently around two third of the global cohort of eligible girls lack access to HPV vaccination. Therefore, this intervention is likely to improve access to HPV vaccine and reduce health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health,	*Inter-vention*	*Com parison*	*Both*	*Neit her*	*Un-clear*	Most stakeholders accept HPV vaccine introduction in national immunization programmes.	

	Immunization Managers)?	☒	☐	☐	☐	☐		
	Which option is acceptable to target group?	*Inter-vention* ☒	*Com parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☐	HPV vaccine is generally well accepted among target groups and their parents, However, in some geographies, vaccine hesitancy and rumours on the effect of the vaccine like infertility or other alleged AEFIs have affected vaccine uptake. Data from a study from Tanzania among participants (Mitchell et al 2021 10.1016/j.tvr.2021.200217) indicated that most participants entrusted decisions about the number of HPV vaccine doses to experts. Random allocation to the different dose groups did not feature highly in the decision to participate in the trial. Given a hypothetical choice, girls generally said they would prefer fewer doses in order to avoid the pain of injections. Parental views were mixed, with most wanting whichever dose was most efficacious. Nonetheless, a few parents equated a higher number of doses with greater protection.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Un-certain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	As of March 2022, 117 countries have introduced HPV vaccine in the national immunization schedule. Many countries have also successfully implemented multi age cohort catch up strategies during the introduction years.	

			Coverage varies by region and country and many countries, both higher- and lower income, have been able to achieve good coverage, at least with the first dose. (Bruni et al., 2021)		
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

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Recommendation (text)	• To achieve the goals of the global strategy for cervical cancer elimination, SAGE recommends HPV vaccination for the primary target of 9-14-year-old girls, prior to sexual debut. National immunization programmes can use either a two-dose or a single-dose vaccination schedule. • The option of a single-dose HPV vaccination schedule for routine and multi age cohort (MAC) catch-up vaccination in the primary target population is based on the very high vaccine efficacy of a single dose of HPV vaccine (97.5%) in girls up to 20 years of age observed in a high-quality RCT. • This *off-label* option is recommended from a public health perspective because it provides comparable and high levels of individual protection, while being more efficient (fewer doses per cancer case prevented), easier to implement and less resource-intensive than a two-dose schedule. Modelling based on a single dose schedule predicts that the resulting herd protection would largely compensate for any theoretical difference in efficacy compared with two doses. If a single dose schedule allows higher population coverage, then it has the potential to avert more cases of cervical cancer. • A single-dose schedule can be considered for HPV vaccine products for which satisfactory efficacy and/or immunobridging data for a single-dose schedule are available. New and pipeline vaccines should generate evidence on peak and 24-month immunogenicity bridged to vaccines with proven single-dose efficacy. • Since the single-dose efficacy data comes from a RCT and post RCT follow up study involving girls up to age 20 years, either a two-dose or one-dose schedule can also be used for the vaccination of those who are 15-20 years old. • For those older than 20 years, a reduced, two-dose schedule (instead of 3 doses previously) with a minimum interval of 6 months between doses can be used. Data on immunogenicity and efficacy

	from a post RCT follow up study gives confidence that this reduced-dose schedule will provide protection. • It is uncertain whether immunocompromised individuals will be protected adequately by reduced dose schedules. Until further evidence is available, immunocompromised persons, irrespective of age, should be prioritized and should receive at least two doses but ideally three doses if programmatically feasible. • SAGE recommends as a priority adequately powered trials with reduced dose schedules in immunocompromised individuals to generate evidence on the immunogenicity, efficacy and duration of protection, including on the serum antibody titer response in individuals who have received a single-dose HPV vaccine prior to HIV seroconversion. • Additional evidence should also be generated on reduced-dose schedules in boys and older females and males, and implementation research carried out to improve HPV vaccine coverage. • For global equity and considering the improving supply situation, SAGE recommends all countries urgently introduce the HPV vaccine for the primary target of 9-14-year-old girls and, where feasible and affordable, to prioritize catching-up missed girls through multi-age cohort (MAC) vaccination. Introducing the vaccination of boys and older females should be postponed until the global supply situation is fully unconstrained.
Implementation considerations	SAGE is deeply concerned about the low HPV vaccine coverage in many countries and the gap with the 2030 90% coverage target needed for elimination. The ultimate aim of the HPV vaccination programme should be to reach the highest level of population protection and vaccine coverage among girls before they become 15 years of age with at least one dose of HPV vaccine, irrespective of the schedule. Multiple opportunities should be created to allow girls at any age before 15 years to receive at least one dose and catch up to ensure highest possible population protection.

Monitoring and evaluation	WHO recommends the continuous monitoring of immunization coverage. To measure the impact on cancer incidence, cancer registries should be strengthened.
Research priorities	• Evidence on reduced dose schedules of HPV vaccine for immunocompromised and HIV+ populations, including on the HPV immune response in individuals who received a single dose prior to HIV seroconversion; • Evidence for new and pipeline vaccines on immunobridging to vaccines for which efficacy data on single dose is available, at both peak titre and at 24 months; • Implementation research to improve HPV vaccine coverage, including among HIV+ populations.

Annex 1: Table 1.4. GRADE evidence profile for single dose HPV vaccine compared with no vaccine for HPV infection, seroconversion, and antibody titers (Source: Systematic review Cochrane Response, 2022)

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: short term follow-up, 18 months											
1 RCT	not serious[1]	not serious	not serious	not serious[2]	none	2/985 (0.2%)	36/473 (7.6%)	**RR 0.03** (0.01 to 0.11)	74 fewer per 1000 (from 75 fewer to 68 fewer)	⊕⊕⊕⊕ High	Kenya1 (KEN-SHE), bivalent (Cervarix) and nonavalent (Gardasil 9), 15-20 years old at vaccination
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[3]	not serious	not serious	not serious[2]	none	2/3369 (0.1%)	56/2282 (2.5%)	**RR 0.03** (0.01 to 0.10)	24 fewer per 1000 (from 24 fewer to 22 fewer)	⊕⊕⊕◯ Moderate	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMTs following one dose ranged from 5.73 to 320.43.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMT following one dose ranged from 4.79 to 81.92.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1

CI: confidence interval; **HPV:** human papillomavirus; **RCT:** randomized controlled trial; **RR:** risk ratio

1. Not downgraded despite some concerns with missing outcome data, estimates from unpublished data of modified intention-to-treat analysis of participants HPV naive at baseline.
2. Not downgraded for imprecision due to large effect estimates, despite few events.
3. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.

World Health Organization

Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[25]

Question: Should an *off label*[26], *permissive* one dose HPV vaccine schedule for use in the routine and/or multi-age cohort (MAC) catch up strategies be recommended?

Population: Main population is pre-adolescent and adolescent girls (9-14 years old), but boys and older adults are also included.
Intervention: Single dose vaccination; bivalent (Cervarix and Cecolin), quadrivalent (Gardasil), and nonavalent vaccines (Gardasil 9).
Comparison(s): 2 doses of HPV vaccination
Outcome:
Clinical outcome: including, but not limited to invasive cervical, vaginal, vulval, anal, penile or head and neck cancer; cervical intraepithelial neoplasia (CIN) grade 3+; CIN2+; histological and cytological abnormalities; anogenital warts; high risk HPV infection (genotype-specific prevalence, incidence and/or persistence)
Immunological outcome; seroconversion or seropositivity; geometric mean titers (GMT) of HPV antibodies

Background: As of March 2022, 117 countries introduced HPV vaccine in their national immunization schedules, but these countries represent only a third of the global population of girls and 40% of the global burden of cervical cancer.

In October 2019, SAGE reviewed the evidence on a single dose of HPV vaccines to protect 9-14-year-old girls, the primary target population, against cervical cancer. SAGE concluded the quality and amount of evidence was insufficient for this policy decision and that the evidence from the purposefully designed single dose randomized control trials (RCTs) was required to inform policy

[25] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[26] *The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.*

decisions. Several of the RCTs and effectiveness studies designed to assess single dose schedules have started to generate interim results during 2021.

In November 2020, the World Health Assembly adopted the Global Strategy towards the elimination of cervical cancer. The strategy calls on each country to introduce HPV vaccination by 2030 and set a target of 90% of girls fully vaccinated with HPV vaccine by age of 15. HPV vaccine coverages are below the target of 90% in the majority of countries and the observed high drop out between the first and the second dose indicate programmatic challenges.

Programmatic challenges to introducing the vaccine include high cost and supply constraints. The latter have affected in particular Low and Middle income countries since 2018 and led to delayed introductions and delayed or canceled multi age cohort catch up strategies in GAVI eligible countries.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	HPV infection with oncogenic HPV types causes an estimated 604,000 cases of cervical cancer worldwide (Globocan, 2020). HPV infection also causes a proportion of cancers of the anus, the oropharynx, the vulva and vagina, and of the penis. Of HPV-associated cancers, HPV types 16 and 18 are associated with 85% of HPV-related head and neck cancers and 87% of anal cancers – the second and third most frequent HPV-related cancers with, respectively, 38 000 and 35 000 estimated cases per year. Martel et al., Int. J. Cancer: 141, 664–670 (2017) VC 2017 Anogenital HPV infection can result in benign skin and mucosal tumors, including anogenital warts in men and women. The estimated median annual incidence of new anogenital	

					warts was 137 per 100 000 men and 121 per 100 000 women. (Patel H et al. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases, 2013;13:39)	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☒	*Yes* ☐	*Varies* ☐	Recent data show that single dose HPV vaccine is highly efficacious (VE > 95%) in a RCT among 15 to 20 year old population (Kenshe RCT, Barnabas et al. 2021), and showed similar efficacy compared to 2 or 3 doses of HPV vaccine in 10-18 year old girls in a post RCT follow up study (IARC India, 2021, Basu et al. 2021). See the summary table of Systematic Review by Cochrane Group. (see the Cochrane Systematic Review) Modeling suggests that under an elimination scenario (all countries introduce by 2030 and 90% of girls vaccinated with 2 doses of HPV vaccine by age15) vaccination can prevent more than 61 million cases of cervical cancer over the next century (Brisson 2020). If future evidence from RCTs comparing 1 vs 2 doses do not confirm non-inferiority and 1 dose would have marginally lower protection at individual level, higher one dose coverage and any resulting herd protection would likely result in a larger public health impact (Prem, Brisson 2021).	

					Future improvements in quality and coverage of cervical cancer screening and treatment programmes may mitigate any lower protection from a single dose. There is no immune correlate of protection. Direct evidence on the duration of protection exists for the time vaccines have been licensed (2006). There is evidence that the immune response is stable for a period up to 11 years for a single dose (Costa Rica, CVT data. Kreimer et al., 2020). Similar to other schedules (2 or 3 dose), it is unknown whether a booster dose is beneficial.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Since licensure in 2006, over 500 million doses of HPV vaccines have been distributed. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses. No other serious adverse reactions have been identified and HPV vaccines have an excellent safety profile (GACVS 2017). The safety of HPV vaccine has been confirmed by GACVS and informed by data from large, high-quality datasets from post surveillance systems (see the GACVS Report). https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety Furthermore, by reducing the number of doses to a single dose the existing risk will be diminished.	

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Balance between benefits and harms	*Favours inter-vention*: ☐ *Favours com-parison*: ☐ *Favours both*: ☒ *Favours neither*: ☐ Unclear: ▱		The benefits of protection against all HPV related diseases, cervical but also other forms of cancers and genital warts, outweigh any harm that may arise from vaccination (e.g., pain during immunization, AEFIs)	
What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies*: ☐ *Very low*: ☐ *Low*: ☒ *Mod-erate*: ☐ *High*: ☐ Safety of the intervention *No included studies*: ☒ *Very low*: ☐ *Low*: ☐ *Mod-erate*: ☐ *High*: ☒		As per the Grade table (attached) The quality of evidence on non-inferiority (1 vs 2 doses (IARC India post RCT follow up, Basu et al., 2021 and CVT; Kreimer et al 2020) is low. However, VE outcomes are comparable to high quality 0 vs 1 dose RCT data (Kenshe RCT, Barnabas et al.2021). A growing number of lower quality observation studies confirm the findings from intervention studies. Studies that apply buffer periods in the analysis (excluding participants that did not have sufficient time between vaccination date and outcome measurement date) and studies which adjusted for the most confounding (i.e., studies at the least risk of bias) were more likely to report smaller differences in effect between one and two doses. The very high and comparable efficacy (97.5%) from high quality single dose 0 vs 1 RCT lend further weight.	

							(see the Cochrane Response Systematic Review) High quality safety data based on large, high quality datasets from post-marketing surveillance systems https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability*	*Possibly important uncertainty or variability*	*Probably no important uncertainty or variability*	*No important uncertainty or variability*	*No known undesirable outcomes*	There is no uncertainty about the value placed on prevention of cervical cancer and high acceptance of the vaccination as indicated by high coverage achieved in many programs (Bruni et al., 2021) There is uncertainty about the duration of protection because no direct evidence on the duration of protection beyond 16 years (for several decades) exists for HPV vaccines and there is no immune correlate of protection. There is evidence that the immune response is stable for a period up to 11 years for a single dose (Costa Rica, CVT RCT. Kreimer et al 2020). Similar to other schedules (2 or 3 dose), it is unknown whether a booster dose is beneficial. In some geographies vaccine hesitancy and fear of infertility or other alleged AEFIs affects vaccine uptake. While the risk of infertility, or observed rare conditions such as CRPS or POTS, are not uncertain (*there is no increased risk or*	
		☐	☐	☒	☐	☐		

							causal link to HPV vaccination according to GACVS), it has proven to strongly affect vaccine uptake and acceptance of some programmes. The existence of - or the potential development of - high performing cervical cancer screening and treatment programmes using high quality tests, may mitigate any residual risk or lower protection after a single dose	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Large benefits can be obtained relative to the potential undesirable effects. Reducing the number of required doses to a single dose while obtaining a similarly large benefits in terms of cancer cases averted is preferred by vaccinees as well as by immunization programmes. It leads to reduction in individual and programme level costs while further reducing the risk of pain and AEFIs.	
RESOURCE USE	Are the resources required small?	*No* ☐		*Un-certain* ☐	*Yes* ☒		*Varies* ☐	HPV vaccine is relatively costly compared to traditional vaccines. In addition, vaccine delivery cost has been demonstrated to be high for HPV vaccines. (Jit. M, 2021.https://doi.org/10.1016/j.jval.2020.07.012) A reduction from two doses to a single dose per eligible girl will lead to considerable programme savings. Supply constraints have affected programme options (WHO Global HPV market study Nov 2020)	.

						From an immunization programme perspective, the intervention will not require additional costs and lead to cost reductions in vaccines, human resource time and complexity (registration, tracking). From the perspective of the beneficiaries, adolescent girls and parents, a single dose will reduce any financial costs due to transportation and other opportunity costs.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Cost effectiveness studies have shown that HPV vaccine is cost-effective intervention in various country settings (Abbas et al., 2020.) . These cost effectiveness data are not only based on older vaccine prices (average HPV dose price is going down) but also based on the need for 2 doses. Cost effectiveness of a single dose schedule is therefore higher.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	Currently, two thirds of the global cohort of eligible girls lack access to HPV vaccines. They live in low- and middle-income countries that represent 60% of cervical cancer disease burden. A single dose can lead to earlier access to HPV vaccines (more girls can be reached with the current limited supply of vaccines in the short run) as it would reduce supply constraints. By making HPV introduction more affordable for low-income countries, immunization programmes may decide to advance introductions and protect more girls earlier, thereby reducing health inequities.	

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ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention*: ☒ *Comparison*: ☐ *Both*: ☐ *Neither*: ☐ *Unclear*: ☐	A small-scale informal survey among EPI programmes from low and middle income setting with current and planned HPV programmes (survey carried out between July and October 2021 for WHO SAGE) indicated that a majority would consider adoption of a one dose recommendation for MAC on programmatic grounds. This survey did not ask specifically about a scenario to lower the routine cohort to 1 dose. SAGE & WHO policy endorsement was mentioned as an important criterion for NITAG decisions.	.
	Which option is acceptable to target group?	*Inter-vention*: ☐ *Comparison*: ☐ *Both*: ☒ *Neither*: ☐ *Unclear*: ☐	A study from Tanzania among participants in a 1 vs 2 dose trial (Mitchell et al., 2021 10.1016/j.tvr.2021.200217) indicated that most participants entrusted decisions about the number of HPV vaccine doses to experts. Random allocation to the different dose groups did not feature highly in the decision to participate in the trial. Given a hypothetical choice, girls generally said they would prefer fewer doses in order to avoid the pain of injections. Parental views were mixed, with most wanting whichever dosing was most efficacious. Nonetheless, some parents equated a higher number of doses with greater protection.	
FEASIBILITY	Is the intervention	*No* *Probably* *Uncer* *Probably* *Yes* *Varies*	As per March 2022, 117 countries have introduced HPV vaccine in the national immunization programme at 2- or 3 doses	

	feasible to implement?	*No* □ *tai n* □ *Yes* □ □ ☒ □	schedules successfully. Single dose vaccine programmes would be easier and more efficient. In the informal survey among EPI programmes from low and middle income setting with current and planned HPV programmes carried out between July and October 2021 for WHO SAGE, a majority considered 1 dose vaccination feasible. Experience with reduction in the HPV vaccine schedule exists. Following a policy change in 2014 (WHO HPV position paper, 2014) nearly all countries in the world switched successfully from 3 to 2 dose routine schedules, most within 3 years.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

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Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	• To achieve the goals of the global strategy for cervical cancer elimination, SAGE recommends HPV vaccination for the primary target of 9-14-year-old girls, prior to sexual debut. National immunization programmes can use either a two-dose or a single-dose vaccination schedule. • The option of a single-dose HPV vaccination schedule for routine and multi age cohort (MAC) catch-up vaccination in the primary target population is based on the very high vaccine efficacy of a single dose of HPV vaccine (97.5%) in girls up to 20 years of age observed in a high-quality RCT. • This *off-label* option is recommended from a public health perspective because it provides comparable and high levels of individual protection, while being more efficient (fewer doses per cancer case prevented), easier to implement and less resource-intensive than a two-dose schedule. Modelling based on a single dose schedule predicts that the resulting herd protection would largely compensate for any theoretical difference in efficacy compared with two doses. If a single dose schedule allows higher population coverage, then it has the potential to avert more cases of cervical cancer. • A single-dose schedule can be considered for HPV vaccine products for which satisfactory efficacy and/or immunobridging data for a single-dose schedule are available. New and pipeline vaccines			

should generate evidence on peak and 24-month immunogenicity bridged to vaccines with proven single-dose efficacy.

- Since the single-dose efficacy data comes from a RCT and post RCT follow up study involving girls up to age 20 years, either a two-dose or one-dose schedule can also be used for the vaccination of those who are 15-20 years old.

- For those older than 20 years, a reduced, two-dose schedule (instead of 3 doses previously) with a minimum interval of 6 months between doses can be used. Data on immunogenicity and efficacy from a post RCT follow up study gives confidence that this reduced-dose schedule will provide protection.

- It is uncertain whether immunocompromised individuals will be protected adequately by reduced dose schedules. Until further evidence is available, immunocompromised persons, irrespective of age, should be prioritized and should receive at least two doses but ideally three doses if programmatically feasible.

- SAGE recommends as a priority adequately powered trials with reduced dose schedules in immunocompromised individuals to generate evidence on the immunogenicity, efficacy and duration of protection, including on the serum antibody titer response in individuals who have received a single-dose HPV vaccine prior to HIV seroconversion.

- Additional evidence should also be generated on reduced-dose schedules in boys and older females and males, and implementation research carried out to improve HPV vaccine coverage.

- For global equity and considering the improving supply situation, SAGE recommends all countries urgently introduce the HPV vaccine for the primary target of 9-14-year-old girls and, where feasible and affordable, to prioritize catching-up missed girls through multi-age cohort (MAC) vaccination.

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	Introducing the vaccination of boys and older females should be postponed until the global supply situation is fully unconstrained.
Implementation considerations	• SAGE is deeply concerned about the low HPV vaccine coverage in many countries and the gap with the 2030 90% coverage target needed for elimination. The ultimate aim of the HPV vaccination programme should be to reach the highest level of population protection and vaccine coverage among girls before they become 15 years of age with at least one dose of HPV vaccine, irrespective of the schedule. Multiple opportunities should be created to allow girls at any age before 15 years to receive at least one dose and catch up to ensure highest possible population protection.
Monitoring and evaluation	WHO recommends the continuous monitoring of immunization coverage. To measure the impact on cancer incidence, cancer registries should be strengthened. A proximal health outcome that can be monitored to evaluate the impact of a single dose regime could be the incidence of genital warts if vaccines protecting against HPV types 6 and 11 are used.
Research priorities	• Evidence on reduced dose schedules of HPV vaccine for immunocompromised and HIV+ populations, including on the HPV immune response in individuals who received a single dose prior to HIV seroconversion; • Evidence on reduced dose schedules of HPV vaccine in boys and older populations; • Evidence for new and pipeline vaccines on immunobridging to vaccines for which efficacy data on single dose is available, at both peak titre and at 24 months; • Further evidence on the duration of protection (immunogenicity) and efficacy induced by HPV vaccines in the longer term and impact on health outcomes (pre-cancers and invasive cancers); • Implementation research to improve HPV vaccine coverage, including among HIV+ populations.

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Annex 1 Grade Table 1 vs 2 doses (source: Systematic Review, Cochrane Response 2022)

Single dose HPV vaccine systematic review

Evidence profile 2: Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses

Table 2.7. GRADE evidence profile for single dose HPV vaccine compared with two doses for HPV infection, seroconversion, and antibody titres

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[1]	not serious	not serious	serious[2]	none	2/3369 (0.06%)	8/4199 (0.19%)	**RR 0.32** (0.07 to 1.48)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕◯◯ Low	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% and following two doses 97% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% and following two doses 81.1% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.11 to 0.67 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1
Geometric mean titres (GMT) for HPV 18: follow-up 6 to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.17 to 1.07 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1

CI: confidence interval; **HPV**: human papillomavirus; **RCT**: randomized controlled trial; **RR:** risk ratio

1. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.
2. Downgraded one level due to imprecision, few events and a 95% confidence interval that encompasses a benefit, no effect, and a harm.