Department of Health & Social Care (https://www.gov.uk/government/organisations/department-of-health-and-social-care)

Independent report

JCVI statement on a one-dose schedule for the routine HPV immunisation programme

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Background

The Joint Committee on Vaccination and Immunisation (JCVI) is an expert scientific advisory committee which advises the UK government on matters relating to vaccination and immunisation.

The committee has been considering the mounting evidence about protection from a single dose of HPV vaccine since 2018 and has been considering the issue of a potential change in the vaccine schedule to one dose of the HPV vaccine during this time. The first major review of a one-dose schedule took place in June 2020.

After a further review of the latest evidence on one-dose schedules in December 2021 the committee issued an interim statement for consultation on 10 February 2022. See the JCVI interim statement (https://www.gov.uk/government/publications/single-dose-of-hpv-vaccine-jcvi-interim-advice) on extending HPV vaccination to adolescent boys.

At that time the committee agreed that there was now enough evidence to advise a change in the schedule from 2 doses to one dose of HPV vaccine in the routine adolescent programme for children and young people aged up to (and including) 14 years of age. This advice was interim, pending a stakeholder consultation. The consultation ran for 6 weeks.

The HPV subcommittee met on 17 May 2022 to review the stakeholders' responses and reported its findings at the June 2022 JCVI meeting. JCVI considers it is now ready to conclude its advice on this issue and this statement sets out the key aspects and final conclusions of the committee.

Stakeholder response to JCVI's interim advice on a one-dose schedule

The JCVI HPV subcommittee met in May 2022 to review and discuss the stakeholder's response to the JCVI's interim advice on a one-dose schedule. See the JCVI website for minutes of the meeting (https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation).

The committee notes that the overall concern cited by stakeholders is that it may be too early to make the decision to change to a one-dose schedule and it may be risky to do this, as the evidence is incomplete with no evidence on duration of protection beyond 12 years. The view of stakeholders is that it would be better to wait until the one-dose trials are complete.

JCVI has made a detailed review of the available evidence and considers that the evidence is now very strong that one dose provides similar protection to that induced by 2 doses. The committee considers that it would not be likely that the picture would change in the next few years. This is because there is already trial and non-trial evidence that initial vaccine efficacy from one dose is very high and

likely comparable to that from 2 doses. In addition, the long duration of protection already seen is associated with a level of antibody that is steady and it is not biologically plausible that the antibody would suddenly fall in the next few years after being sustained for more than 10 years. The one-dose antibody level is associated with high efficacy against persistent infection of HPV vaccine types.

Durability and efficacy of one dose

The Costa Rica Vaccine trial (CVT) and Indian International Agency for Research on Cancer (IARC) studies have shown the durability of one dose of the bivalent or quadrivalent vaccine with stable antibody levels out to 10 to 11 years so far, and with comparable efficacy to that of 3 doses. The JCVI view is that the biology of immunity is consistent with an ongoing persistence of the immune response which has remained unchanged over 10 years and is likely to continue to do so along the same trajectory.

Preliminary data from trials designed to investigate immunogenicity and efficacy of one dose of the 9-valent vaccine or a delayed second dose (the delayed booster study (DEBS)) are showing that the 9-valent vaccine has the same qualities as the bivalent vaccine and quadrivalent vaccine in terms of high efficacy against HPV vaccine types, high rates of seroconversion, and antibody kinetics which show a trajectory of a stable antibody response similar to that observed for the bivalent and quadrivalent vaccines.

The Kenya single-dose HPV-vaccine efficacy (KEN SHE) trial investigated the efficacy of single dose HPV vaccination with the 9-valent vaccine in young African women.

Results showed that:

- adolescent girls and young women were effectively protected from HPV infection over the first 18 months post vaccination
- HPV 16/18 vaccine efficacy (VE) was greater than 97%, which was in keeping with results in the licensure trials for 3 doses
- in the pre-planned efficacy sensitivity analyses, which excluded participants with HPV DNA at 6 months, VE against the 7 HR HPV types in the 9-valent group was 95%
- incidence of the 9 HPV vaccine types was high in this setting (approximately equal to 9 per 100 woman-years) – one-third higher than previous vaccine trials

See Efficacy of single-dose HPV vaccination among young African women (https://pubmed.ncbi.nlm.nih.gov/35693874/).

JCVI has now seen early unpublished data from the Dose Reduction Immunobridging and Safety Study (DoRIS) trial showing the antibody level and trajectory for one dose of the 9-valent vaccine to be stable and follows that seen in

other HPV vaccine studies from month 12 to month 36. There is also no difference in antibody avidity between dose groups and vaccines.

Immunobridging of immunogenicity results from DoRIS to the KEN SHE trial study have shown the one-dose immune response in DoRIS to be non-inferior to KEN SHE where one-dose efficacy was observed at month 18 and demonstrated a VE of greater than 97% against HPV 16/18 and VE of 95% against the 7 high-risk HPV types in the 9-valent group, when efficacy was measured 6 months after the first dose as was done with 2- and 3-dose trials.

The prime-boost paradigm

Stakeholders have highlighted that a one-dose schedule breaks the dogma that a prime and a boost is required for this type of vaccine. The remarkable immunogenicity of the HPV vaccines is likely due to the biology of the virus and the remarkable qualities of the virus like particles (VLPs) in the HPV vaccines. The papilloma virus has not evolved to avoid the serological antibody response and vaccination delivers the VLP antigen via a pathway completely different to that for natural infection whereby the virus gains entry via the mucosa. The structure and geometry of the VLP is such that neutralising epitopes are optimally arranged and presented. The HPV VLP is also a very rigid and stable structure providing a sustained presentation to the immune system.

The switch to one dose can be advised now and there should be sufficient lead-in time before this happens. If policy decision is in agreement with JCVI advice the earliest date indicated is the academic year 2023 to 2024.

Males

Stakeholders have also pointed to the lack of evidence on one dose in boys and on the impact on non-cervical cancers. JCVI notes that data on immunogenicity and efficacy for a single dose in boys was very limited. That had also been the situation for 2 or 3 doses although it has been subsequently shown that males have a similar antibody response to girls for 2 doses. Infection in males at most sites is the same as in females via the mucosa. Based on these observations, the JCVI view is there is currently no reason to doubt that protection will be the same in boys as it is for girls.

Global advice

Stakeholders also cited the potential impact outside the UK of JCVI’s advice to move to one dose and that the World Health Organization (WHO) had not recommended this. On this point, the view of stakeholders has been superseded by a review of the data by WHO, which reaches broadly the same conclusions as the JCVI analysis. JCVI notes that the WHO Strategic Advisory Group of Experts on Immunization (SAGE) met in April 2022 to evaluate the evidence that has been emerging over past years that single-dose schedules provide comparable efficacy to the 2- or 3-dose regimens. SAGE’s review concluded that a single-dose HPV

vaccine delivers solid protection against HPV, the virus that causes cervical cancer, that is comparable to 2-dose schedules. SAGE recommended updating dose schedules for HPV as follows:

- 1- or 2-dose schedule for the primary target of girls aged 9 to 14
- 1- or 2-dose schedule for young women aged 15 to 20
- 2 doses with a 6-month interval for women older than 21

Immunocompromised individuals, including those with HIV, should receive 3 doses if feasible, and if not, at least 2 doses.

See WHO press release (https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer).

Manufacturer's response

JCVI noted the view of the 9-valent vaccine manufacturer, Merck Sharp and Dohme (MSD), which is that there is currently too much uncertainty and ambiguity about the one-dose schedule and that further data were needed. MSD was also given the opportunity to present to the HPV subcommittee. The points raised by MSD and the discussion of the issues raised are available in the minutes of the May HPV 2022 subcommittee meeting (see the JCVI website for minutes of the HPV meeting (https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation)).

Modelling

As part of the presentation by MSD, JCVI reviewed modelling work by Daniels and others (see Modeling the health and economic implications of adopting a one-dose 9-valent vaccination regimen (https://www.sciencedirect.com/science/article/pii/S0264410X22002201)) and funded by the manufacturer. JCVI notes that the model includes some strong assumptions that protection from one dose is always less than that from 2 doses and efficacy declines exponentially. JCVI notes, however, that there are real data to suggest that efficacy may not be less from one dose compared with 2 doses and that efficacy stays high initially and does not start to drop immediately as modelled by MSD.

JCVI notes a letter submitted by an international group of HPV modellers to the journal 'Vaccine' raising concerns about the assumptions and methodology in the modelling paper by Daniels and others – see Recent economic evaluation of 1-dose HPV vaccination uses unsupported assumptions (https://www.sciencedirect.com/science/article/pii/S0264410X22009100). More detail on the JCVI's discussion of the paper by Daniels and others is available in the minutes of the HPV subcommittee and JCVI June meeting.

At the June JCVI meeting JCVI reviewed modelling work by Professor Marc Brisson using the HPV ADVISE model which indicated that a switch to a one-dose routine HPV vaccination was not predicted to substantially increase cervical cancers if duration of protection is greater than 20 years. If one-dose protection was to wane within the next 10 years (at which time more than 20 years of follow-up will be available), switching back to 2-dose routine vaccination could mitigate losses in cervical cancer prevention.

The model also showed that even in the most pessimistic scenarios the impact of a shorter waning of protection would be quite far into the future and that there would be data from ongoing clinical trials available long before then to show if there was a problem with one dose that required action. In view of this, JCVI noted that the modelling provided reassurance to those who were concerned about potential future waning, and highlighted the importance of communicating, as with all vaccine programmes, that the committee will undertake ongoing review of the programme which would pick up any new data that indicated a change was required, many years before waning was translated into an increase in cancer risk.

Coverage, inequalities and monitoring

JCVI notes stakeholders' concerns that a one dose has the potential to lead to a drop in coverage and widen health inequalities. JCVI agrees that with a move to a one-dose schedule it will be important to enhance efforts to vaccinate anyone missed first time round and health inequalities should be closely monitored as they should be for all other vaccination programmes. Some of the resources freed up due to the reduction in vaccination sessions should be re-directed to interventions that strengthen programme delivery, increase coverage rates and reduce inequalities. This might best be undertaken by ensuring vaccination contracts included a requirement for extra mop-up visits to drive maximum opportunity for uptake.

A key element of the surveillance of the programme in England is monitoring for type-specific infection in residual samples of young women undergoing Chlamydia screening. As the prevalence of HPV16/18 has now fallen below 1% for the routine cohort, larger numbers might be required to screen. A change in prevalence would be a key signal of loss of protection. The committee agrees that monitoring for the programme should continue to be via the surveillance of HPV prevalence, and the cohorts should be large enough to have adequate power to see a change. The surveillance of anogenital warts should also provide an early indicator of an unexpected decline in protection.

JCVI notes that evidence will continue to accumulate from the ongoing trials. In addition to the DoRIS, KEN SHE and DEBS studies JCVI notes that globally there are many other studies looking at one dose including: HOPE (South Africa), HANDS (The Gambia), PRIMAVERA, ESCUDO and PRISMA (Costa Rica) and a community effectiveness study in Thailand.

JCVI considers emerging evidence from these ongoing trials will be key data sources. JCVI notes these trials are ahead in time of a potential move to one dose in the UK and they will provide an early warning of any waning in protection of a one-dose schedule.

Conclusions and advice

The advice on one dose can be finalised. The switch can be advised now and there should be sufficient lead-in time before this happens. If policy decision is in agreement with JCVI advice the earliest date indicated is the academic year 2023 to 2024, but the timing and implementation of a potential one-dose programme is a tripartite decision between UKHSA, NHS England and DHSC and the responsibility of the devolved administrations for Scotland, Wales and Northern Ireland.

The committee agrees that this advice applies to both males and females. WHO SAGE advice for one dose was up to and including the age of 20 which was based on the evidence that efficacy was as strong in older teenagers up to 20 years of age from the KEN SHE trial. The latter was despite a lower antibody response compared with younger adolescents. In the routine adolescent programme eligibility for vaccination remains until the 25th birthday and the JCVI view is that vaccine efficacy will not differ for a 20-year-old compared with someone aged between 21 to 25 years old, though the benefits of vaccination are less in older ages compared with younger ages.

JCVI, therefore, advises the following schedules for the HPV programme:

- a one-dose schedule for the routine adolescent programme and MSM programme before the 25th birthday
- a 2-dose schedule from the age of 25 in the MSM programme
- a 3-dose schedule for individuals who are immunosuppressed and those known to be HIV-positive

Monitoring and surveillance

JCVI agrees that the following actions will be necessary if the government decides to accept its advice and implement a one-dose schedule:

- the importance of monitoring the programme for impact, coverage and inequalities
- a strong surveillance package to continue to monitor the incidence and prevalence of anogenital warts and high-risk HPV infections in the population

- the importance of catching those girls and boys who miss their dose once the move to one dose is implemented, by ensuring there are additional opportunities in school for vaccination
- the importance of relaying the message of continuing to have screening appointments regardless of vaccination status

JCVI is an independent departmental expert committee and a statutory body that advises the UK government and devolved administrations. JCVI advice is evidence driven and derived from expert opinion. JCVI did not consider the cost of the programme in assessing the evidence or coming to the decision. JCVI's advice is aimed at maximising the health benefits from vaccination on the basis of the cost effectiveness of vaccination. The latter ensures that the NHS can make the best use of its resources, aiming to deliver the maximum health benefit to the population in a fair, consistent and justifiable way. JCVI will look at new evidence as it emerges from the clinical trials and the monitoring and surveillance of the UK programme. The clinical trials are ongoing and will be ahead of any potential implementation and will continue to provide high quality evidence on the durability of the protection of one dose. JCVI has reviewed modelling which suggests there would be a long lead-in time under a pessimistic scenario of waning protection with which to take appropriate action were this to be the case. JCVI will continue to keep its advice under close review and take appropriate action where necessary.

Appendix: evidence

The following is evidence JCVI considered in forming its advice.

See also JCVI interim statement (https://www.gov.uk/government/publications/single-dose-of-hpv-vaccine-jcvi-interim-advice/jcvi-interim-advice-on-a-one-dose-schedule-for-the-routine-hpv-immunisation-programme) on extending HPV vaccination to adolescent boys.

Evidence on efficacy and duration of one dose of the bivalent and quadrivalent vaccine

A post hoc analyses of randomised control trials (RCTs).

Bivalent vaccine

Kreimer AR, Rodriguez AC, Hildesheim A and others. Proof-of-principle evaluation of the efficacy of fewer than 3 doses of a bivalent HPV16/18 vaccine (https://pubmed.ncbi.nlm.nih.gov/21908768/). J Natl Cancer Inst. 2011;103(19):1444–1451.

Kreimer AR, Struyf F, Del Rosario-Raymundo MR and others. Efficacy of fewer than 3 doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica vaccine and PATRICIA trials

(https://pubmed.ncbi.nlm.nih.gov/26071347/). Lancet Oncol 2015; 16: 775–86.

Kreimer AR, Sampson JN, Porras C and others. Evaluation of durability of a single-dose of the bivalent HPV vaccine: the CVT Trial (https://pubmed.ncbi.nlm.nih.gov/32091594/). J Natl Cancer Inst. 2020 Feb 24. pii: djaa011.doi: 10.1093/jnci/djaa011

Tsang S, Sampson JN, Schussle J and others. Durability of Cross-Protection by Different Schedules of the Bivalent HPV Vaccine: The CVT Trial (https://academic.oup.com/jnci/article/112/10/1030/5753954): The CVT Trial. J Natl Cancer Inst (2020) 112(10): djaa010. doi: 10.1093/jnci/djaa010

Quadrivalent vaccine

Sankaranarayanan R, Prabhu PR, Pawlita M and others. Immunogenicity and HPV infection after one, 2 and 3 doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study (https://pubmed.ncbi.nlm.nih.gov/26652797/). Lancet Oncol 2016; 17: 67–77.

Sankaranarayanan R, Joshi S, Muwonge R and others. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study (https://pubmed.ncbi.nlm.nih.gov/29551226/). Vaccine. 2018;36(32 Pt A):4783–4791

Basu P, Malvi SG, Joshi S, Bhatla N, Muwonge R, Lucas E and others. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, 2 and 3 doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study (https://doi.org/10.1016/S1470-2045(21)00453-8). The Lancet 326 Oncology 2021;22:1518–29.

Evidence on Immunogenicity and efficacy on one dose of the 9-valent vaccine from clinical trials

Barnabas RV, Brown ER, Onono MA and others. Efficacy of single-dose HPV vaccination among young African women (https://pubmed.ncbi.nlm.nih.gov/35693874/). NEJM Evid. 2022 Jun;1(5):EVIDoa2100056. doi: 10.1056/EVIDoa2100056. Epub 2022 Apr 11. PMID: 35693874; PMCID: PMC9172784.

Baisley KJ, Whitworth HS, Changalucha J and others. A dose-reduction HPV vaccine immunobridging trial of 2 HPV vaccines among adolescent girls in Tanzania (the DoRIS trial) (https://pubmed.ncbi.nlm.nih.gov/33421649/). Study protocol for a randomised controlled trial. Contemp Clin Trials. 2021 Feb;101:106266. doi: 10.1016/j.cct.2021.106266. Unpublished data presented to JCVI in December 2021 and HPV subcommittee in May 2022. Minutes available on JCVI website (https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation).

Zeng Y and others, Moscicki AB, Sahasrabuddhe VV and others, Prospective, single-arm, open-label, nonrandomized, phase IIa trial of a nine-valent prophylactic HPV vaccine to assess immunogenicity of a prime and deferred booster dosing schedule among 9 to 11 year old girls and boys – clinical protocol

(https://pubmed.ncbi.nlm.nih.gov/30935375/). BMC Cancer 2019 19:290. Unpublished data presented to JCVI in December 2021. Minutes available on JCVI website (https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation).

Systematic reviews and observational studies of HPV vaccine effectiveness by number of doses

Henschke N, Bergman H, Brian Buckley B and others. Efficacy, effectiveness and immunogenicity of one dose of HPV vaccine compared with no vaccination, 2 doses, or 3 doses (https://www.sciencedirect.com/science/article/pii/S0264410X19316597); Cochrane Response systematic review presented to WHO SAGE (https://terrance.who.int/mediacentre/data/sage/SAGE_Slidedeck_Apr2022.pdf)

Markowitz LE, Drolet M, Perez N and others. Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs (https://pubmed.ncbi.nlm.nih.gov/29802000/). Vaccine. 2018;36(s32Pt A):4806–4815.

Brotherton JM, Budd A, Rompotis C and others. Is one dose of human papillomavirus vaccine as effective as 3?: A national cohort analysis (https://pubmed.ncbi.nlm.nih.gov/31319173/). Papillomavirus research (Amsterdam, Netherlands). 2019;8:100177.

Rodriguez A M, Zeybek B, Vaughn M and others. Comparison of the long-term impact and clinical outcomes of fewer doses and standard doses of human papillomavirus vaccine in the United States: a database study. (https://pubmed.ncbi.nlm.nih.gov/32037524/) Cancer 2020;126(8):1656-1667. doi: 10.1002/cncr.32700. Epub 2020 Feb 10.

Verdoodt F, Dehlendorff C, Kjaer SK. Dose-related effectiveness of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia: a Danish nationwide cohort study (https://pubmed.ncbi.nlm.nih.gov/30892587/). Clin Infect Dis. 2020;70(4):608–14

Sonawane K, Nyitray AG, Nemutlu GS and others. Prevalence of human papillomavirus infection by number of vaccine doses among US women (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2757996). JAMA network open. 2019;2(12):e1918571.

Markowitz LE, Naleway AL, Klein NP and others. Human papillomavirus vaccine effectiveness against HPV infection: evaluation of one, 2 and 3 doses (https://academic.oup.com/jid/article/221/6/910/5648192?login=false). The Journal of Infectious Diseases. 2020;221(6):910-918.

Zeybek B, Lin YL, Kuo YF, Rodriguez AM. The impact of varying numbers of quadrivalent human papillomavirus vaccine doses on anogenital warts in the United States: a database study (https://pubmed.ncbi.nlm.nih.gov/29762430/). J Low Genit Tract Dis 2018; 22: 189–94.

Toh ZQ, Russell FM, Reyburn R and others. Sustained antibody responses 6 years following 1, 2 or 3 doses of quadrivalent human papillomavirus (HPV) vaccine in adolescent Fijian girls, and subsequent responses to a single dose of bivalent HPV vaccine: a prospective cohort study (https://pubmed.ncbi.nlm.nih.gov/28034886/). Clin Infect Dis. 2017;64(7):852–859.

Whitworth H S, Gallagher K E, Howard N and others. Efficacy and immunogenicity of a single dose of human papillomavirus vaccine compared to no vaccination or standard three and two-dose vaccination regimens: A systematic review of evidence from clinical trials (https://www.sciencedirect.com/science/article/pii/S0264410X19316597). Vaccine. 2020;(38)1302–1314.

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