Independent report

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

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Introduction

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 JCVI has been considering the issue of a potential move to one dose of the HPV vaccine for several years. Indeed, the committee was aware of the potential for one dose as far back as 2018.

The first major review of a one-dose schedule took place in June 2020 and although the evidence considered indicated the direction of travel was towards a one-dose schedule the committee agreed that it would like to see more data, particularly on the 9-valent vaccine, before providing advice on the HPV programme.

JCVI met in December 2021 to consider the latest evidence on the protective efficacy and immunogenicity of one dose of HPV vaccine including that from ongoing clinical trials of a single-dose schedule using the 9-valent vaccine.

JCVI considers it is now ready to issue interim advice on a move to a one-dose schedule for the routine adolescent programme. This statement sets out the key considerations and evidence supporting the conclusions and advice of the committee.

Background

Overview

In 2008 following a detailed review of the impact and cost-effectiveness of a routine HPV vaccination programme in adolescents aimed at reducing the burden of HPV-associated cervical cancer, JCVI recommended a universal programme of 3-dose HPV vaccination in girls aged 12 to 13 years in schools, along with a catch-up programme for girls aged from 13 to under 18 years (JCVI, 2008). The bivalent vaccine Cervarix® was the HPV vaccine offered from September 2008 to August 2012 with the quadrivalent vaccine Gardasil® being offered from September 2012, both as 3-dose courses. After a review of the data by JCVI, this was revised in 2014 to a 2-dose course for the routine programme for girls up to and including the age of 14 years old. As a result of further JCVI advice in 2015, a programme for men who have sex with men (MSM) up to and including the age of 45 years old was introduced in 2018 (after piloting in 2016) and the addition of 12 to 13 year old boys to the routine programme was introduced in September 2019 following advice made in 2018. In 2020, following the emergence of new evidence showing the potential for a single dose of vaccine in young adolescents, the committee started the process of reviewing the data to consider a change in advice for the routine programme.

The current school-based routine HPV immunisation programme has been highly successful in consistently achieving very high levels of uptake (>80%) prior to the pandemic. Although there have been interruptions to the delivery of the programme during the pandemic the programme has built up a substantial level of herd protection in the population after more than 13 years of vaccination. The addition of boys to the routine programme has strengthened and added resilience to the gains already accrued.

Early evidence of the impact of the national HPV immunisation programme on cervical cancer in England has shown substantial reductions of 87% and 97% in the incidence of cervical cancer and CIN3, respectively, in young women who were offered the bivalent Cervarix vaccine at age 12 to 13 years after the introduction of vaccination (Falcaro and others, 2021). These findings suggest that the HPV vaccine will save hundreds of lives (and eventually thousands) every year in the UK.

Move from 3 to 2 doses

In February 2014, based on advice from the HPV subcommittee, JCVI concluded that a 2-dose schedule in adolescents could be recommended up to (and including) 14 years of age for both Cervarix and Gardasil. A 2-dose schedule of Gardasil® was implemented in the national programme for the routine vaccination cohort of females aged 11 to 13 years old (academic Year 8 in England and Wales) from September 2014.

The HPV subcommittee's advice on the move to 2 doses was that:

- a decision could be made based on the serological data
- the serological data were convincing enough for the JCVI to recommend a 2-dose schedule for adolescent girls for either of the currently available vaccines
- it would be very important to closely monitor vaccine uptake to ensure coverage remains high for the second dose
- there should also be the contingency to give a third dose later in life if emerging evidence shows a waning of immunity in the population that warrants an additional dose

The JCVI noted that:

- protection was almost exclusively antibody mediated with the protective threshold undefined but substantially below that detected by routine assays – persisting even after apparent antibody disappearance, as demonstrated for HPV18 in Gardasil®-immunised women
- the duration of protection in adolescents vaccinated using a 2-dose schedule administered as a prime boost (separated by a minimum of 6 months) was likely to be the same as a 3-dose schedule
- the closest example to the waning of protection for the HPV vaccine was likely to be that observed for the hepatitis A vaccine, where protection is at least 25 years and may be lifelong
- the modelling and cost effectiveness study comparing a 2-dose schedule with a 3-dose schedule indicated that a third dose would no longer be cost effective provided that the duration of protection of a 2-dose schedule lasted for at least 20 years

Previous considerations on a one-dose schedule

In February 2020 JCVI noted evidence on the immunogenicity and efficacy of bivalent and quadrivalent vaccines when offered as a single dose.

The committee agreed that the data presented, provided compelling evidence that a single dose of vaccine could be sufficient to provide good and long-lasting protection when offered in early adolescence. The committee agreed that a call for evidence should be issued to ensure all available information was considered by the committee, before advising on any change to the national immunisation programme.

A call for evidence was issued on 18 March 2020 (https://www.gov.uk/government/consultations/single-dose-of-hpv-vaccine-call-for-evidence-from-the-jcvi) and the JCVI HPV subcommittee was convened on 21 May 2020 to consider the evidence submitted and advise the committee on whether the evidence was sufficient to advise a move towards a single-dose vaccination programme.

The outcome of the HPV subcommittee's considerations (JCVI HPVSC, May 2020) and advice were reported to the main committee on 3 June 2020:

- due to the disruption caused by the COVID-19 pandemic the priority for the delivery of the routine HPV immunisation programme was for all eligible children to receive at least the first dose of the HPV vaccine. Delivery or catch-up of the second dose should be considered at the appropriate time according to local planning
- there was no compelling reason to continue with 3 doses in those aged over 15 and the programme should move to a 2-dose schedule for those ages, including MSM at a suitable time
- the committee agreed that the evidence considered indicated the direction of travel was towards a one-dose schedule and there was confidence in the data showing equivalent efficacy between one and 2 doses for the bivalent and quadrivalent vaccines but lack of data for the 9-valent vaccine
- before potentially concluding its advice the committee would like to see further data, particularly for HPV9. The committee would revisit the International Agency for Research on Cancer (IARC) study data at the next data cut-off point and look to emerging immunogenicity data on the 9-valent vaccine as well as new data and evidence from elsewhere
- it would like feedback from Public Health England (now the UK Health Security Agency (UKHSA)) and NHS England on the planning implementation and delivery of a potential one dose programme and what might be optimal

The evidence considered included published and unpublished data on the immunogenicity and efficacy of a single dose of bivalent, quadrivalent and 9-valent HPV vaccine, and the duration of antibody response following vaccination. The evidence strongly indicated that one dose of the bivalent or quadrivalent vaccine will provide protection against infection and clinical endpoints for more than 10 years. Modelling evidence considered also showed that a one-dose schedules was likely to provide almost as much health benefit as a 2-dose schedule even in pessimistic scenarios where the one-dose schedule has lower efficacy or duration of protection. Evidence regarding the durability of the antibody response to 9-valent vaccine was more limited given that this was a more recently introduced vaccine.

At the June 2020 JCVI meeting the committee agreed with the HPV subcommittee's advice that there was enough evidence to support a single-dose schedule for the bivalent and quadrivalent vaccines, and it would like to see more data on the 9-valent vaccine, before providing advice on the HPV programme.

The committee agreed that it should be possible to decide on a single dose 9-valent schedule based on immunogenicity data alone, and there was the potential to conclude their advice on this issue in the next one to 2 years.

The committee also agreed that there should be excellent protection from a single dose in the short to medium term, and this should be prioritised on resumption of the programme which had been interrupted by the COVID-19 pandemic.

JCVI issued its advice in a statement on the delivery of the HPV vaccine during COVID-19 (https://www.gov.uk/government/publications/delivery-of-the-hpv-vaccine-and-impact-of-school-closures-statement-from-the-jcvi), in July 2020.

Evidence considered by JCVI

Evidence on efficacy and duration of one dose of the bivalent and quadrivalent vaccine – post hoc analyses of randomised control trials (RCTs)

Two longstanding trials have contributed valuable data with post hoc analyses of non-randomised data on the potential of one dose the Costa Rica Vaccine Trial (CVT) (bivalent vaccine) and the IARC Indian trial (quadrivalent vaccine). These have published end points followed up out to 10 years and have shown persistence of antibody and efficacy over time.

In the CVT study approximately 7,500 women aged 18 to 25 years old were randomised to receive 3 doses of bivalent vaccine or a control vaccine in 2004 to 2005 but 20% received fewer than 3 doses:

- after 4 years of follow-up, vaccine effectiveness (VE) estimates against persistent infection for one dose were non-inferior to 3 or 2 doses (Kreimer and others, 2011)
- the one-dose VE findings were confirmed in the GSK-sponsored PATRICIA trial (Kreimer and others, 2015)
- a 4-fold decrease in antibody titres was observed comparing the one and 3 dose groups, but antibody levels from one dose remained stable over 4 years and were 10-fold higher than those from natural infection
- the lower antibody levels from one dose did not appear to translate into inferior protection with no decrease in VE when comparing one with 3 doses
- follow-up continued with a new control arm added (Gonzalez and others, 2015) and 11 years after vaccination, one-dose VE against point prevalence HPV vaccine type infection was non-inferior to 3 doses, (Kreimer and others, 2020)
- robust cross protection against HPV types 31/33/45 was also observed at 11 years for one dose which was non inferior to 3 doses (Tsang S and others, 2020)
- attack rates for non-carcinogenic HPV type infections were comparable in the control and vaccinated groups (and by dose group within the HPV arm) suggesting similar risk for acquisition of the HPV vaccine types by group;
- antibody titres in one-dose recipients remained stable and did not decline over the 11 years
- a more thorough assessment of antibody results showed between year 9 and year 11 antibody did not decrease. The distribution of the change in antibody levels between year 9 and 11 indicated that an anamnestic response to exposure was unlikely to be responsible for the robust duration of response

The IARC study was initiated as a RCT in 2009 to compare 2 versus 3 doses in 10 to 18 year old unvaccinated unmarried girls with plans to recruit 10,000 girls for each arm of the study across 9 sites. The trial had been stopped by the Indian government after a safety scare due to events occurring in another trial. When the RCT was halted over 4,000 girls had received a single dose with roughly similar numbers receiving 2 doses (0, 2 months), 2 doses (0, 6 months) and 3 doses (0, 2 and 6 months). The dosage groups were comparable by age distribution and demographic characteristics.

Follow-up of those vaccinated was allowed to continue and unvaccinated comparison cohorts were added post hoc to estimate efficacy in the different dose groups. Results have showed:

- antibody titres to HPV16/18 for the different doses, as measured using the Luminex ligand binding assay, indicated an inferior response for single dose compared with 2 or 3 doses. However, antibody kinetics were similar, with an early increase in titre, followed by a decline and plateau, with antibody levels remaining stable out to 48 months. The more sensitive neutralisation assay (PBNA) showed a similar picture, and stability at 60 months was higher than the mean antibody titre in unvaccinated women (Sankaranarayanan and others, 2018)

- for persistent infections of HPV 16/18, a high level of protection was observed after 10 years of follow-up, and no difference was observed by dose number. Unvaccinated women had a 24 times higher proportion of persistent infection than vaccinated women (2.4% vs 0.1%)
- adjusted vaccine efficacy for one dose against incident and persistent HPV 16/18 infections, after exactly 10 years of follow up, was non-inferior for one dose compared to 2 or 3 doses, and very high against persistent infection at 93·1% (77·3 to 99·8) (2,135 women assessed) in the single dose cohort compared with 93·1% (77·3 to 99·8) (1,452 women assessed) and 93·3% (77·5 to 99·7) (1,460 women assessed) in the 2-dose and 3-dose cohorts respectively (Basu and others, 2021)
- cervical screening results to date indicated a very low incidence of infection but the study intends to continue follow-up of participants in the study until at least 2026, to demonstrate durability of protection and antibody persistence over 15 years. By then robust data from 50,000 cervical samples would be available
- the study also contributed to the JCVI's advice to move from 3 to 2 doses in those aged 15 years and over by demonstrating antibody and neutralising antibody titres were non-inferior in 15 to 18 year old girls who received 2 dose of vaccine compared with girls of the same age who received 3 doses. The same strong antibody response was observed for both groups with non-inferiority for effectiveness in terms of both incident infection and persistent infection (Basu and others, 2019)

Joint modelling conducted by 4 modelling groups (London School of Hygiene and Tropical Medicine, Public Health England, University of Laval, Harvard University) suggested that one-dose vaccination has similar health benefits to a 2-dose programme. Population-level health benefits were only slightly reduced even if the efficacy of a one-dose vaccine against HPV infection was as low as 80%, or if the duration of protection was 20 or 30 years, while a 2-dose schedule gave lifelong protection if efficacy was assumed to be 100% (Prem and others, 2021).

New evidence on one dose considered by JCVI at the December 2021 JCVI meeting

In December 2021 the JCVI reviewed data presented from the following studies:

1. The Dose Reduction Immunobridging and Safety Study (DoRIS) a randomised immunogenicity, safety and immunobridging trial of one dose of the 9-valent and bivalent HPV vaccines in Tanzanian girls (Baisley and others, 2021).
2. The KEN SHE trial looking at the efficacy of single dose HPV vaccination in young African Women (Barnabas and others, 2021).
3. The delayed booster study (DEBS): a prospective, single-arm, open-label, non-randomised trial on the immunogenicity of a prime and delayed booster dosing schedule of the 9-valent vaccine in the United States (Zeng and others, 2019).
4. An update to the systematic review of observational studies of HPV vaccine effectiveness by number of doses, conducted as part of the Single-Dose HPV Vaccine Evaluation Consortium.

The DoRIS trial

The primary objectives of the DoRIS study were to demonstrate non-inferiority of HPV 16/18 seroconversion after one dose compared with 2 or 3 doses of the same vaccine (bivalent and 9-valent) at month 24; and non-inferiority of HPV 16/18 antibody geometric mean titre (GMT) at month 24, comparing one dose in DoRIS with historical efficacy cohorts who received only one dose. Secondary objectives include comparing HPV 16/18 antibody avidity and memory B cell responses between dose regimens and vaccines, evaluate antibody levels of the HPV genotypes in the 9-valent vaccine and evaluate the impact of malaria on antibody GMTs. The results presented from the DoRIS study showed:

- seropositivity was >97.5% across all doses of both vaccines
- antibody levels by dose, vaccine, and trajectories over time followed those seen in other HPV vaccine studies including one dose observational studies
- no difference in antibody avidity was observed between dose groups within the same vaccine
- all immunobridging objectives were met; one dose immune responses in DoRIS were non-inferior to those in historical cohorts where one dose efficacy had been observed

Further data and analyses are awaited including the Luminex ligand binding assay results at month 24 for the other 7 high risk (HR) HPV vaccine types, antibody results at month 36 and 60, and immunobridging with the KEN SHE trial at month 24.

The KEN SHE trial

The KEN SHE trial investigated the efficacy of single dose HPV vaccination with the 9-valent vaccine in young African women. Primary end points were to test:

- efficacy of 9-valent and bivalent vaccine against incident persistent HPV16/18 infection
- efficacy of 9-valent vaccine against incident persistent HPV 16/18/31/33/45/52/58 infection

Results showed that (Barnabas and others, preprint 2021):

- 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 >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 (~9/100 woman-years) – one-third higher than previous vaccine trials

It was noted that the rigorous design, high fidelity to the protocol, high retention and clear ascertainment of outcomes provided strong evidence for single-dose HPV vaccine efficacy. The next step proposed by the investigators would be a blinded crossover vaccination to evaluate durability.

The delayed booster study (DEBS)

This was a prospective, single-arm, open-label, non-randomised trial on the immunogenicity of a prime and delayed booster dosing schedule of the 9-valent vaccine with participants receiving the second dose (delayed booster) at 24 months.

The objective of the study was to determine the persistence and stability of serologic geometric mean titres (GMT) of HPV16/18 and HPV 31/33/45/52/58/6/11 between 6, 12, 18, and 24 months after the prime dose and prior to the administration of the second dose of the 9-valent HPV vaccine in a cohort of 200 girls and boys in Arizona and California.

Preliminary analyses demonstrated that anti-HPV16 and anti-HPV18 GMTs, measured by the HPV VLP IgG ELISA, remained stable and persistent between 12, 18, and 24 months after receipt of a single dose of the 9-valent HPV vaccine.

Preliminary subset analyses at 6, 12, 18 and 24 months for the measurement of anti-HPV16/18/31/33/45/52/58/6/11 by a multiplex binding assay (based on Merck total IgG LIA) were presented in confidence. The committee noted that neutralization assays and antibody avidity measurements were underway.

Antibody levels at 6-monthly visits up to 24 months (before delayed booster) will also be immuno-bridged to future immunological and efficacy outcomes from randomised trials evaluating single-dose schedules. A longer-term immunogenicity evaluation after delayed booster dose is also currently underway.

A systematic review of observational studies of HPV vaccine effectiveness by number of doses

This study was conducted as part of the Single-Dose HPV Vaccine Evaluation Consortium. This review of post-licensure effectiveness studies was published in 2018 summarising the evidence (Markowitz and others, 2018), previously presented to the committee (May 2020 HPV subcommittee, June 2020 JCVI meetings), had now been updated to August 2020.

Thirty-two publications from 10 countries were reviewed. Eight evaluated effectiveness against HPV infection, 9 anogenital warts, and 15 cervical cytological or histological abnormalities. Three types of bias were assessed selection, information and confounding to rate the overall bias. Investigators attempted to control for or stratify by potentially important variables, such as age at vaccination. Some studies used buffer periods or wash out to control for prevalent infection at time of vaccination. Data was summarised in a narrative synthesis and results showed that:

- most studies were assessed to be at moderate or serious risk of bias
- most studies found differences in effectiveness by number of doses
- effectiveness estimates increased and differences between dose groups decreased in analyses limited to younger age at vaccination, or when using longer buffer periods
- more recent studies, with analyses stratified by age at vaccination or restricted to younger age groups, found more similar effectiveness estimates by number of doses (Brotherton and others, 2019; Rodriguez and others, 2020; Verdoodt and others, 2020)

The conclusions of the study were that:

- age at vaccination impacts vaccine effectiveness; buffer periods can help address, but do not eliminate, bias due to differences in age at vaccination and potential prevalent infection at the time of vaccination between dose groups
- studies examining persons vaccinated prior to sexual activity and using methods to reduce bias are needed for valid interpretation of observational data

- the results illustrated why there have been conflicting results between studies and the importance of age at vaccination and made the argument for younger age at vaccination against HPV

Additional data to come

Further data is expected from the DoRIS, DEBS and KEN SHE trial. In addition to this the committee notes that the ESCUDDO trial which is a formal non-inferiority trial comparing one to 2 doses plus a non-randomised observational cohort of zero doses to compute efficacy has plans for an early readout based on 3 to 4 years of follow up by 2024.

Both the CVT and IARC studies will continue to be followed for immunological and efficacy endpoints and report the latest data cuts in the next few years.

Conclusions and advice

In June 2020 the committee was convinced by the data on one dose of the quadrivalent or bivalent vaccine which showed that:

- most decay in antibody from HPV vaccination occurs in the first 6 to 8 months post-vaccination and then plateaus
- antibody then remains stable and has been observed to remain so for more than 10 years
- one dose efficacy remains high and is as good as that observed for 2 or 3 doses. It was hypothesised that the ordered, repetitive and dense display of epitopes by the virus like particles (VLPs) in the vaccines explained why the vaccines were so highly immunogenic and remarkably potent (Schiller and others, 2018, Slifca and others, 2019)

However, as the UK programme was moving to using the 9-valent vaccine reassurance was needed that this vaccine would have similar characteristics when used as a single dose. The committee now has these reassurances in the data for the 9-valent vaccine which indicate that a one-dose schedule for the 9-valent vaccine is likely to offer high efficacy against all the included types just like the 2 other vaccines.

The committee is of the view that the level of evidence for a move to a single dose is compelling and is at a similar if not greater level (as it includes efficacy data) to that supporting the move from 3 to 2 doses which was previously advised. This evidence now also includes robust shorter-term efficacy data for the 9-valent vaccine and sustained and consistent immunogenicity data that allows immuno-bridging from the quadrivalent to the 9-valent vaccine.

Therefore, the committee has agreed that there is now enough evidence to advise a change in the schedule from 2 doses of HPV vaccine to one dose in the routine adolescent programme for children aged up to (and including) 14 years of age. This advice is interim pending a stakeholder consultation.

The move to the 9-valent vaccine is due to commence in the current year. The 9-valent HPV vaccine is JCVI's preferred vaccine for the programme because of the additional protection that is provided against the 5 additional cancer-causing HPV types. The 9-valent HPV vaccine should therefore protect against >90% of the cervical cancers caused by the HPV high risk types, an increase from the 70 to 80% of cervical cancers that the bivalent and quadrivalent vaccines protect against (Mesher and others, 2015).

A single-dose schedule should free up funding and resources that can be deployed to strengthen the adolescent immunisation programmes. It should simplify the vaccine schedule and reduce the needle burden in adolescents. Furthermore, a single-dose schedule is likely to be more acceptable to the

population. On the other hand a move to one dose and a single vaccination visit in schools may reduce the opportunity, compared with the current programme, to catch-up those who miss their HPV dose the first time round and this has the potential to widen inequalities in uptake. This should be mitigated by increased capacity for follow up of those who miss their HPV vaccine when it is first offered. Some of the resources made available due to the reduction in vaccination sessions should be re-directed to interventions that strengthen programme delivery, increase coverage rates and reduce inequalities.

Current efforts are focused on the ongoing catch-up of those adolescents who have missed their first or second dose due to the interruptions to the schools' immunisation programme by the pandemic. Sufficient lead in time will be required to plan and operationalise the transition to a one-dose schedule in the adolescent programme by NHS England and the devolved administrations. As with all vaccine programmes, a one-dose HPV programme will be closely monitored though surveillance and kept under review by the committee with the option of adjusting the programme if new data emerges or if new vaccines or technologies become available that could further strengthen protection against HPV infection and the consequent cancers.

The committee will continue to review new data as this becomes available during the coming decade from the various studies mentioned above. Besides virological surveillance, real world data will also continue to accrue through the monitoring of rates of genital warts which are almost exclusively caused by HPV 6 and 11 and have a much shorter natural history from infection to disease.

Invitation to stakeholders

As with some recent important decisions on the HPV programme, the JCVI is issuing these interim findings for consultation to ensure that the most appropriate and up-to-date evidence has been used, and that reasonable assumptions have been made where evidence is limited or unavailable.

Responses should be sent to jcvi-consultation@phe.gov.uk by 11.45pm on 24 March 2022.

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