Royal Society for Public Health response to the Joint Committee on Vaccination and Immunisation (JCVI) consultation on "JCVI interim advice on a one-dose schedule for the routine HPV immunisation programme"

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1.About the Royal Society for Public Health

Royal Society for Public Health (RSPH) is an independent health education and campaigning charity, committed to improving and protecting the public's health and wellbeing. We are the world's longest-established public health body with over 5000 members who are committed to supporting the public's health. Our activities include providing qualifications, e-learning, accreditation and programmes. We also campaign on a wide range of issues to support better health and wellbeing for the public.

2.Key recommendations

We recommend JCVI delays publishing this interim advise as final until the results of clinical trials are peer reviewed and published. The evidence currently available are from studies with moderate to high risks of bias and only suggest, do not confirm, that one-dose of the HPV vaccine could be effective.

We recommend JCVI carefully considers the cost-effectiveness of this change. Studies from other European countries demonstrate that offering two doses for boys and girls is cost-effective and reduces cases of cervical, penile, anal and head and neck cancers, as well as genital warts.

We emphasise that changing the programme to a single-dose scheme would increase health inequalities. Children and young adults living in deprivation are already less likely to come forward for the HPV vaccination programme and would have even fewer opportunities to catch up if only one dose was offered.

3.Extraordinary results of the current programme

The HPV vaccination programme in the UK is a remarkable success. Research demonstrated it reduced the incidence of cervical cancer by 87% in women in their 20s in England[1], and results were praised by the Global Alliance for Vaccines and Immunisations (GAVI) as a demonstration of the real value of vaccinations[2].

HPV vaccination proves that a disease can be almost eliminated with a simple intervention. **We cannot risk losing these gains without clear evidence about the effectiveness of this one-dose scheme in the "real" world.**

4.Evidence currently available is not sufficiently robust

As explained in JCVI meeting minutes from 15th December 2021, new evidence was presented to the committee, and was used to validate interim advice. But there are some areas of concern:

- Most of the studies considered have so far analysed bivalent and quadrivalent vaccines and involved girls and young women only
- What was considered as new evidence were randomised control trial protocols, not efficacy data
- There is no sufficient data for boys or men who have sex with men (MSM)
- Using data that has not been peer reviewed can and will impact the validity and quality of evidence used for making such an important decision with potential ramifications that could de-rail gains already made with the HPV vaccination programme
- The DoRIS clinical trial (Baisley et al, 2021) started in 2021 and is yet to be finished. Published results are partial and only 155 girls have received one dose[3]
- The KEN SHE clinical trial (Barnabas et al, 2021) had only its study protocol published. Participants will continue follow-ups for the tstudy until December 2022, with analysis and dissemination of results in 2023[4]
- The systematic review JCVI used to inform its decision concluded, amongst other things, that "variation in effectiveness by number of doses was observed across all endpoints (prevalence, anogenital warts and cervical abnormalities)"[5]
- The Costa Rica ESCUDDO trial has recently published its research protocol and is yet to make its preliminary results available. Despite its importance, only girls are enrolled in the trial[6]
- One of the studies included by JCVI as evidence concluded that "data on long term protection beyond 7 years against HPV infection and cervical precancerous lesions are needed before policy guidelines regarding a single dose can be formulated and implemented"[7].

The World Health Organisation (WHO) does not currently recommend one dose. In 2019 it commissioned a study to the Cochrane Response evaluating the efficacy of one dose of licensed HPV vaccines. They concluded that "for most outcomes there is insufficient evidence to determine whether there is a difference between one dose of HPV vaccine and two or three doses, and what evidence is available is at high risk of bias"[8]. Markowitz and others (2018) also highlighted that most of the studies assessed in their review had a moderate or high risk of bias[5].

Given the lack of robust evidence, **we recommend JCVI delays publishing this interim advise as final until the results of clinical trials are peer reviewed at least and preferably published.** Data available is from studies with moderate and high risks of bias and only suggest that one-dose could be effective.

5.Cost-effectiveness of the vaccination programme

According to its Code of Practice, JCVI is committed to analysing the cost effectiveness of vaccination programmes. Cervical cancer alone cost the NHS over £21m in 2011[9]. This number does not include expenditures with anal, penile and head and neck cancers, neither does it include treatment costs for genital warts. The success of the HPV vaccination programme shown in 2021 demonstrated how it could alleviate the NHS from further pressure.

The financial burden of cancer is not exclusive to the NHS: families are also hit with women losing their incomes and having higher care expenses. Added to this is the unmeasurable cost on women's and their families' mental health.

Studies carried out in other European countries have proven the cost-effectiveness of the 9-valent HPV vaccine offered in a two-dose scheme. A dynamic transmission model study in Italy offering two doses of Gardasil 9® showed[10]:

- further reductions of 17% in the incidence of cervical cancer
- 35 and 14% reduction in anal cancer for males and females respectively
- over a million cases of genital warts avoided after 100 years
- switching to the nine-valent vaccine further reduced the burden associated to cervical cancer and HPV-related diseases was highly cost-effective.

Similar findings were shown by research carried out in Germany[11]. Using the same methods, the model estimated that:

- anal cancer incidence was reduced by 12% and 29% in females and males, respectively
- universal coverage with two doses of the 9-valent vaccine had considerable health benefits and cost savings in all diseases considered.
- a wider societal perspective may yield additional advantages, as HPV-related diseases are associated with productivity losses.

A study carried out in Austria also using dynamic transmission model demonstrated that:

- two doses of the 9-valent vaccine offered to boys and girls were cost saving and cost effective.

However, their suggested coverage threshold was below the numbers advised by the World Health Organisation[12].

In Spain, the dynamic transmission model calibrated to this country's epidemiological reality using two doses gender neutral of 9-valent vaccine resulted in[13]:

- further reductions in the number of cases of disease and deaths
- potential to reduce the burden of HPV-associated disease in men, irrespective of their sexual orientation
- cost-effectiveness exceeding the Spanish threshold.

Belgium assessed two dose gender-neutral 9-valent HPV vaccines at a 90% coverage rate. The dynamic transmission modelling indicated that[14]:

- 9-valent HPV vaccination in both males and females demonstrated greater cumulative reductions in HPV-related diseases
- the cumulative incidence of anal, penile, and head and neck cancers decreased in males
- the incidence of genital warts was projected to decrease by 60.1% 35.9% cases in males and females living in Flanders, respectively
- the incidence of genital warts was projected to decrease by 63.1% 65.2% cases in males and females living in in Wallonia-Brussels, respectively
- the strategy was cost-effective.

A study in the UK concluded that gender-neutral vaccination was also cost-effective versus halted vaccination, taking into consideration bivalent, quadrivalent and 9-valent vaccines, not only the latter[15]. Analysis involving specifically MSM in the UK established that HPV vaccinations are a clinically effective and cost-effective way of reducing the burden of HPV-related disease in MSM, however only the quadrivalent vaccine was entered in the model[16].

We recommend JCVI analyses the impact of gender-neutral two-dose vaccination scheme of the 9-valent vaccine before changing the current programme. Evidence from other countries demonstrate that a two-dose offer is still cost-effective. Its gains are considerable not only for reduction of cervical cancer cases, but for genital warts and anal cancer as well.

6.Potential to increase health inequality

Deprivation is associated with a higher number of cervical cancer cases. Cancer Research UK estimates that[17]:

- cervical cancer incidence rates in England are 65% higher in the most deprived quintile compared with the least (2013-2017)
- around 520 cases of cervical cancer each year in England are linked with deprivation.

Inequality negatively impacts the HPV vaccination programme. Published evidence in the UK has demonstrated that:

- uptake of the HPV vaccine varies by ethnicity[18]
- uptake was significantly lower in more deprived areas[19]
- ethnic composition, early childhood vaccination status, access to cervical screening and primary care quality influence uptake in both routine and the catch-up cohorts[20]
- initiation of HPV vaccination is less likely among girls and young women living in the poorest households, who do not attend school and whose parents are from Black African ethnic backgrounds[21].

Covid-19 undoubtfully compromised the delivery of the vaccination programme, however, many local authorities in England were not reaching 80% coverage for 2 doses among girls before the pandemic. For the 2017-2018 period, 35 Local Authorities (LAs) were below the 80% threshold for girls on year 9 receiving their second dose. For the 2018-2019 period, the number of Local Authorities not reaching the recommended threshold increased to 37. That is 25% of LAs whose data is gathered by the UK Health Security Agency (UKHSA).

The 12 local authorities presented on table 01 (p. 05) have consistently underperformed on the HPV vaccination coverage. Some reached 80% in 2015 – 2016 but were unable to sustain this result. Interestingly, all these LAs find themselves in the list of 20% most deprived areas in England for the 2014-2020 period[22].

Table 01: HPV vaccination coverage on girls (year 9) with two doses

	% girls 13-14 Year Olds (Year 9) vaccinated with two doses				
Local Authority	2015 - 2016[23]	2016 - 2017[24]	2017 - 2018[25]	2018 - 2019[26]	Listed (in no particular order) in the top 20% most deprived areas in England 2014-2020[i]
Barnet	72.6	75.4	75.3	75.1	✓
Birmingham	80.4	75.6	77.2	75.9	✓
Brent	81.0	68.4	66.0	63.2	✓
Cornwall	71.5	57.6	73.1	70.4	✓
Ealing	81.3	67.3	75.2	68.1	✓
Hackney	64.1	78.6	72.2	69.8	✓
Hammersmith and Fulham	77.1	79.7	65.3	61.7	✓
Hillingdon	86.9	78.2	75.9	75.3	✓
Hounslow	83.5	77.5	77.5	75.0	✓
Manchester	79.0	61.6	78.3	75.4	✓
Salford	85.4	77.1	71.1	72.4	✓
Waltham Forest	73.3	65.7	68.8	56.7	✓

As mentioned, Covid 19 significantly aggravated the problem. Due to lockdown, the HPV vaccination programme was halted for 6 months. Its reestablishment has not been free from problems and consequently, 109 Local Authorities in England fell from reaching the 80% recommended coverage.

Understandable circumstances led to 73% of LA missing the coverage target. However, **JCVI's priority now should be in developing advice and strategy to help children and young adults catch up in the scheme and access missed**

[i] This list is the count of the most deprived LSOAs by Local Authority Area. It sums up the number of LSOAs in the top 20% of the Index of Multiple Deprivation for England for each Local Authority in the country.

doses. Changing the advice and recommending one dose will take away from the public opportunities to catch up and will increase health inequalities.

Also, it is well established that deprivation, poverty and ethnic background play a role in access to HPV vaccines. The "Levelling up White Paper" highlighted the UK's vaccine development task force as a remarkable scientific achievement but did not mention how tackling inequalities and programmes to engage the public could enhance people's access to vaccines. **The JCVI is in a privileged position to influence policy making in this matter and assist the levelling up mission, however, by changing the HPV programme to a single-dose offer it will risk levelling the nation down.**

Covid-19 created a window of opportunity for the vaccines debate in the country. More evidence and public discussions helped inform against vaccine hesitancy. Because of the speed of events, JCVI had to streamline its processes and expedite advice formulation to meet public needs. All this was positive, but it cannot compromise the robust and respected processes the Committee developed to guide the nation with their advice regarding vaccines in general. **RSPH considers that the moment is inappropriate for changes in a programme as respected and as impactful as the HPV one**. **Such a speed decision without robust data to back it up could hinder the population's trust in the vaccine and in the JCVI and revert the gains mentioned above.**

7.JCVI work of excellency in past occasions

The Joint Committee has examples of careful analysis that considered the cost-effectiveness of vaccination programmes and their benefits to the public's health in their portfolio; an example being the changes that took place in the meningococcal vaccination programme for children and adolescents.

When analysing if meningococcal B vaccine Bexsero® should be recommended to the country, JCVI took into consideration the epidemiology of the disease, the fact that it is a burden to younger groups, the quality-of-life losses in close family members of those affected by invasive meningococcal and cost of sequalae among those affected. Several studies, many carried out by British institutions such as the University of Birmingham and Warwick University, were taken into consideration by the JCVI.

Not only technical variables were taken into consideration. Minutes from the meeting held in June 2015 describe that the JCVI appraised a study from UCL on parental attitudes to the use of Bexsero®, as a way of understanding their attitudes towards the introduction of this new vaccine[27].

Records demonstrate that the replacement of MenC vaccine by MenACWY conjugate vaccine in adolescents was also carefully analysed by JCVI. **This rushed advice for a single HPV dose does not align with JCVI ways of working and its past record of excellence.** Minutes from the meeting held on the 15th of December

2021 do not clearly explain how the weak evidence presented led to this decision, conflicting with other minutes that clearly show JCVI decision-making process.

8.Lack of clarity on public engagement

JCVI, when publishing its interim advice, mentioned that a single dose would reduce the needle burden in adolescents. There was no explanation as to how the committee came to this conclusion or which evidence was taken into consideration[28].

A literature search run on EBSCOhost using as search terms “needle burden” or needle phobia”, “adolescents or young adults” and “HPV” retrieved no results. When removing HPV as a search term, articles found did not relate to vaccines. If there was public engagement of any sort that helped JCVI analyse the existence of a needle burden amongst adolescents, it was not shared with the wider public. **We recommend the JCVI explains the rationale of this conclusion, since the existence and the impact of this needle burden are unclear.**

The interim advice also mentions that a single-dose schedule is likely to be more acceptable to the population. RSPH questions this conclusion, using the Covid-19 vaccination as an example, when 85.2% of the eligible population (circa 49 million people) have received their second dose.

RSPH agrees that vaccine hesitancy is an important issue and must be taken into consideration when formulating advice, however it should be tackled with information and programmes that address deprivation and health inequalities, not with diminution on the number of doses offered by an already well-know and successful programme such as the HPV one.

Change of advice to one dose could hinder population’s compliance with the HPV vaccine programme. Before the pandemic, coverage for girls on Year 9 having a second dose was above 83% for the 2015 – 2019 period in England. The programme recently changed to welcome boys and MSM into the scheme. **RSPH considers that yet another change, this time without robust evidence or strong public engagement would jeopardise the good general compliance of the population with the HPV vaccination programme. We recommend that Public and Patient Involvement and Engagement in the development of this advice is considered, so that people’s conformity with the scheme is not lost.**

9.Impact to global health

The NHS, its programmes and policies are held as a golden standard to the rest of the world. Many countries draw inspiration from British policies, and decisions made here affect people from different areas of the globe.

The WHO still recommends 2 doses for young people under 15[29]. It is aware that clinical trials are taking place at the moment, after data suggested that a single dose could offer protection, but the Organisation has not changed its guidance and still advises that two doses be offered[30].

Change of advice made without robust evidence from clinical trials could increase the burden of disease, especially in the developing world. Considering that the UK is a role model to other countries, **we strongly recommend JCVI waits for more robust data to be peer reviewed and published, before changing its advice for one dose. Other countries will follow its lead and this decision, if precipitated, could have an immensely negative cascade effect globally.**

This consultation response is submitted by **Dr Fernanda Aguilar Perez**, Policy and Public Affairs Executive, Royal Society for Public Health (RSPH).

Email: faguilarperez@rsph.org.uk

Phone: 020 7265 7327.

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