Continued HPV vaccination in the Face of Unexpected Challenges: A Commentary on the Rationale for an Extended Interval Two-Dose Schedule

Hilary S. Whitworth,[1*] John Schiller,[2] Lauri E. Markowitz,[3] Mark Jit,[4] Marc Brisson,[5] Evan Simpson,[6] and Deborah Watson-Jones[1]

* Corresponding author: hilary.whitworth@lshtm.ac.uk.

Hilary S. Whitworth,
LSHTM
Keppel Street
London
WC1E 7HT

[1] Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK

[2] National Cancer Institute, National Institutes of Health, Maryland, USA

[3] National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA

[4] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

[5] Centre de recherche du CHU de Québec and Department of Social and Preventive Medicine, Université Laval, Quebec, QC, Canada

[6] Center for Vaccine Innovation and Access, PATH, Seattle, USA

Disclaimer: The content, findings, and conclusions of this report are those of the authors, and do not necessarily represent the official position of their agencies or institutions of employ.

All authors attest they meet the ICMJE criteria for authorship.

Existing HPV vaccines are highly effective for prevention of HPV infection, the leading cause of cervical cancer and a significant cause of many other oral and anogenital cancers[1]. World Health Organization (WHO) has recommended including HPV vaccination of girls in national immunization programs since 2009[2] and, in 2018, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization agreed that vaccination is the most critical intervention for cervical cancer elimination[3]. As of May 2020, 41% of low-and-middle income countries and 81% of high-income countries had introduced HPV vaccination[4]. Whilst a number of barriers exist to HPV vaccination programs, the worldwide HPV vaccine shortage is a current obstacle due to increasing demand. Expanding production capacity will take several years[5].

In 2019, concerns that a shortage may result in some countries failing to introduce or sustain the recommended HPV vaccination program (two doses delivered at 0 and 6-12 months in immunocompetent adolescents aged <15 years) prompted SAGE to advise countries to consider alternative vaccination strategies if faced with an imminent vaccine shortage[2]. One such strategy is an extended-interval, two-dose schedule with the first dose administered to girls aged 9-10 years and the second dose 3-5 years later. Delaying the second dose would enable countries to commence or continue national HPV vaccination programs with reduced short-term vaccine demand until vaccine manufacturers can increase production. Another emerging issue in the HPV vaccine policy context is the current COVID-19 pandemic caused by the SARS-CoV-2 virus, which has disrupted many immunization activities. An extended-interval HPV vaccination schedule may assume even greater importance as countries make decisions on how to adapt or suspend current or planned vaccination activities to minimize contact between vaccinees and healthcare workers.

This commentary discusses the biological plausibility and epidemiological evidence for an extended interval vaccination strategy, and considerations for use during the HPV vaccine shortage and COVID-19 pandemic.

Biological plausibility of extended interval HPV vaccination schedules

The first HPV vaccine dose is a priming dose; antigen is free to circulate and eventually bind to naïve B cells with B-cell receptors (BCRs) that specifically recognize it. This interaction is key to activation of B cells, leading to their proliferation and differentiation into antibody-producing plasma cells. However, induced antibodies can bind to antigen introduced by a later booster vaccine dose, and thus inhibit activation of additional naïve B cells and cognate memory B cells generated by the prime. Antibody titers rapidly decay 6–12 months after a vaccine dose, so booster doses are generally delayed to allow systemic antibody concentrations to fall below levels that substantially inhibit interactions with cognate B cells. Antibody titers tend to decay more slowly after a year or, in the case of the HPV vaccine, stabilize at a plateau level[1]. New naïve B cells are constantly produced, and memory B cells generally persist for many years. Therefore, delaying a booster dose by several years should not impair the secondary response, and could even improve responses if circulating antibody titers continue to decline.

This prediction is borne out in studies of hepatitis A vaccine (HAV), the licensed vaccine that most closely resembles HPV vaccines structurally and immunologically. HAV is comprised of chemically inactivated hepatitis A virions and induces consistent and durable antibody responses, even after a single dose (as observed with HPV VLP vaccines), apparently because the inactivation does not unduly disrupt the high density of repetitive virion surface epitopes recognized by virion antibodies. HAV is routinely delivered in two doses six months apart, but multiple studies in adolescents and adults have shown that

delaying the second dose for 2–6 years does not reduce antibody responses to the boost[6]. Thus, it is plausible to expect similar responses to delayed boosting with HPV vaccines.

Evidence regarding immunogenicity, effectiveness, impact, and cost-effectiveness of extended-interval schedules of HPV vaccines

Evidence supporting SAGE's recommendation of extended-interval HPV vaccination in the context of a vaccine supply shortage was drawn, in part, from a Cochrane Systematic Review that compared longer and shorter intervals in a two-dose schedule, conducted in September 2018[7]. Evidence from four randomized controlled trials (RCTs) (Table 1; #1,2,6,7) suggested that HPV16/18 antibody seropositivity rates and geometric mean titers (GMTs) through 36 months after dose 2 were equivalent or higher with longer compared to shorter intervals. Non-randomized assessments from two additional RCTs (Table 1; #8,10 and Table 2; #1,2) generated similar immunogenicity results, and further demonstrated that the cumulative incidence of HPV16/18 infections over seven years post-vaccination did not increase with longer intervals.

A correlation between level of circulating VLP antibodies, or other vaccine-induced immune responses, and protection has not been established. However, in post-hoc analyses of the CVT and IARC vaccine trials, a single dose of vaccine continues to give protection up to 11 years post-vaccination, despite inducing at least a 4-fold lower plateau antibody titer than the per protocol three doses. Thus, even if use of an extended two-dose schedule resulted in a moderate decrease in antibody response, it is unlikely that it would compromise efficacy.

Results from observational studies were generally consistent with those from RCTs, albeit with a few exceptions. In three studies, point estimates were suggestive of higher risk of cervical abnormalities (Table 2; #3,4) or genital warts (Table 2; #10) with longer dosing intervals, but confidence limits were wide and overlapped with those for shorter dosing intervals. All observational studies were conducted in countries recommending three-dose HPV-vaccination schedules; the girls who received two doses did not complete the series. In these studies, there can be substantial bias because characteristics probably associated, and thus more prevalent, with receiving two instead of three doses and with longer intervals between doses (e.g., lower socio-economic status and education level, reduced healthcare-seeking behaviour, earlier age of sexual debut) are also risk factors for HPV infection. However, since this most likely biases *away* from effectiveness in the longer interval groups, finding similar or lower risk in these groups probably does not alter the interpretation that vaccination is at least as protective with longer compared to shorter dosing intervals.

Further evidence (identified through our own scoping review, conducted in MEDLINE, of evidence published since September 2018) comes from a post-hoc analysis of two intervention studies conducted in Canada (Table 1; #5)[8]. HPV16/18 GMTs were not significantly different post-vaccination in groups with a 6-month versus 3-8-year dosing interval. The study was not prospectively randomized, and the longer dosing interval group was small and likely prone to considerable bias, although these biases were probably more likely to cause a reduction in GMTs in the longer dosing-interval group.

Two mathematical models have independently evaluated a range of HPV vaccination strategies in the context of supply constraints[9, 10]. These strategies varied with regards to age of routine vaccination (9 or 14 years old), sex of target population (female-only or gender-neutral), vaccine schedules (current or extended), number of age-cohorts vaccinated (with or without multi-age cohorts), and number of doses

(one or two). The most efficient and cost-effective strategies were those involving five-year extended intervals between the first and second doses because they allow much of the demand for doses to be delayed until more supplies are available[3].

Considerations for extended interval schedules

If this off-label delivery strategy is to be adopted, countries will need to consider associated challenges, such as the requirement for adequate vaccination records, tracking systems, and communications to facilitate delivering the second dose[2]. Messaging about the risk of HPV infection between doses will require careful consideration. Indeed, SAGE's recommendation highlights the need to consider country context and programmatic feasibility. Nonetheless, an extended interval schedule may offer a viable solution for countries to commence or sustain a national program if the alternative is to not vaccinate girls due to insufficient vaccine supply. Notably, randomised trials are underway to assess efficacy and immunogenicity of single dose HPV vaccination in a number of countries and populations. If these data demonstrate efficacy then they will provide additional assurance for the efficacy of extended intervals even if some countries choose to retain two-dose schedules.

The recommendation concerning extended-interval HPV vaccination has taken on greater significance with the emergence of the COVID-19 pandemic, which has affected public health programs worldwide. Vaccination services and campaigns in some countries are being suspended or postponed as clinics and schools are closed, vaccination resources (e.g., funding and personnel) are being redeployed to the pandemic response, and social distancing and lockdowns are affecting access to vaccination venues. For countries with existing HPV vaccination programs, this may result in delayed initiation of vaccination as well as unplanned interruptions if the second dose cannot be delivered according to schedule. Other

144 countries may have to postpone starting a national HPV vaccination program. An option to deliver HPV
145 vaccination with a planned extended (3-5-year) interval between the first and second doses would reduce
146 the burden on over-stretched health services and reduce person-to-person contact during the pandemic.
147
148 **An opportunity to continue vaccination in the face of unexpected challenges**
149
150 Available data suggest that an extended-interval two-dose HPV vaccination schedule may be as
151 immunogenic and efficacious as currently-recommended schedules, albeit with a paucity of evidence
152 from studies with a dosing interval >12 months. Although immunogenicity studies are mostly small,
153 data-linkage studies are affected by biases, and there are not yet efficacy/effectiveness data from
154 prospectively randomized trials, the biological rationale for an extended dose schedule is compelling and
155 practical justification is strong in the context of vaccine supply constraints. The disruptions caused by
156 the COVID-19 pandemic provide further reason to consider an extended 2-dose interval.
157
158 Existing vaccination recommendations do allow for extended intervals. In practice, an individual who
159 has not completed vaccination within the licensed dosing schedules is recommended to complete, not re-
160 start, the vaccine series. The WHO HPV position paper states that there is no maximum recommended
161 interval, but suggests (in normal circumstances) an interval of up to 12–15 months[3]. The U.S. Advisory
162 Committee on Immunization Practices recommendations state that vaccines should be given as close as
163 possible to the recommended intervals but, with some exceptions (e.g. oral typhoid vaccine), a schedule
164 interruption does not require restarting the series or providing additional doses[11].
165
166 Thus, whilst the rigorously evaluated and widely-accepted 2-dose schedule with a 6-12-month interval
167 remains the gold standard for <15-year-olds, an extended-interval regimen is arguably an opportunity for

continued roll-out or sustained vaccination, where the likely alternative is fewer girls vaccinated. Even if this strategy unexpectedly results in lower individual-level efficacy, the population-level impact of an extended-interval schedule may remain high if it enables more widespread vaccination and greater coverage[12].

Acknowledgements

The authors wish to acknowledge the contribution of the Strategic Analysis, Research & Training (START) Center, Department of Global Health, University of Washington for sharing their systematic review search results, which were used in development of Tables 1 and 2 of this commentary. Support for this commentary was provided by PATH on behalf of the Single-Dose HPV Vaccine Evaluation Consortium, which includes Harvard University, London School of Hygiene & Tropical Medicine, PATH, Université Laval, University of British Columbia, US Centers for Disease Control and Prevention, US National Cancer Institute, and Wits Reproductive Health and HIV Institute.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Schiller, J.T., X. Castellsague, and S.M. Garland, *A review of clinical trials of human papillomavirus prophylactic vaccines.* Vaccine, 2012. **30 Suppl 5**: p. F123-38.
2. *World Health Organization. Weekly epidemiological record. Weekly Meeting of the Strategic Advisory Group of Experts on Immunization, October 2019: conclusions and recommendations.* 2019. **No 47**(94): p. 541-560.
3. *Strategic Advisory Group of Experts (SAGE) on Immunization. Working Group on potential contribution of Human Papillomavirus (HPV) vaccines and immunization towards cervical cancer elimination. Background Document and Report to SAGE.* https://www.who.int/immunization/sage/meetings/2019/october/1_HPV_SAGE2019WG_for_SAGE.pdf, 2019.

4. PATH, *Global HPV Vaccine Introduction Overview. Projected and current national introductions, demonstration/pilot projects, gender-neutral vaccination programs, and global HPV vaccine introduction maps (2006-2023).* https://path.azureedge.net/media/documents/Global_HPV_Vaccine_Intro_Overview_Slides_webversion_2020May.pdf, 2020.
5. Garland, S.M., et al., *IPVS statement on "Temporary HPV vaccine shortage: Implications globally to achieve equity".* Papillomavirus Res, 2020. **9**: p. 100195.
6. Van Damme, P., et al., *Hepatitis A booster vaccination: is there a need?* Lancet, 2003. **362**(9389): p. 1065-71.
7. Bergman H, B.B., Villanueva G, Petkovic J, Garritty C, Lutje V, Riveros-Balta AX, Low N, Henschke N, *Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males.* Cochrane Database of Systematic Reviews, 2019. **CD013479**(11).
8. Gilca, V., et al., *Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post hoc analysis of two clinical trials.* Hum Vaccin Immunother, 2019. **15**(7-8): p. 1980-1985.
9. Brisson, M., et al., *Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States.* J Natl Cancer Inst, 2016. **108**(1).
10. Jit, M., et al., *Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study.* Lancet Glob Health, 2014. **2**(7): p. e406-14.
11. *Centers for Disease Control and Prevention. Timing and spacing of immunobiologics. General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html. 12 February 2020.*
12. Kim, J., *Could 1 dose be less efficacious than 2 doses but still be a great public health intervention?* HPV World. **Y1; No.30**: p. 26-28.

Table 1: Clinical trials and observational studies comparing immunogenicity responses with differing intervals between 2 doses of HPV vaccine. Results are shown for the latest timepoint evaluated after the second HPV vaccine dose for each study.

#	Reference(s)	Study design	Location	Gender; age at vaccination	Vaccine	Antibody responses by interval between dose 1 and 2[b]			
						Interval	N[a]	HPV-16 GMTs (95%CI)	HPV-18 GMTs (95%CI)
1 month after dose 2 / before dose 3									
1	Iversen, JAMA, 2016	RCT	Multinational	M / F; 9-14y	9vHPV	6m, girls	301	8,004.9 (7,160.5-8,948.8)	1,872.8 (1,651.6-2,123.6)
						6m, boys	301	8,474.8 (7,582.4-9,472.3)	1,860.9 (1,641.1-2,110.2)
						12m	300	14,329.3 (12,796.4-16,045.9)	2,810.4 (2,474.9-3,191.3)
2	Neuzil, JAMA, 2011	Cluster RCT	Vietnam	F; 11-13y	4vHPV	2m	205	656.7 (573.2-752.4)	77.2 (66.9-89.0)
						3m	195	880.6 (776.3-998.9)	100.8 (85.9-118.4)
						6m	193	920.6 (747.9-1,133.2)	135.0 (111.8-163.1)
						12m	213	1,581.3 (1,373.1-1,821.1)	191.1 (163.0-224.1)
3	Russell, Vaccine, 2015	Prospective cohort study	USA	F; 9-18y at dose 2 / 3	4vHPV	≤3m	39	133 (97-183)	52 (36-77)
						>3m	126	608 (515-717)	174 (139-218)
4	Widdice, Vaccine, 2018	Prospective cohort study	USA	F; 9-17y at dose 3	4vHPV	51-70d	192	181.4 (160.3-205.3)[c]	42.0 (36.8-48.1)[c]
						≥4m	198	557.4 (493.4-629.8)[c]	105.4 (92.4-120.3)[c]
5	Gilca, Vaccine 2019	Post-hoc analysis of 2 intervention studies	Canada	F; 9-14y and M / F; 9-10y	4vHPV/ 9vHPV[d]	6m	173	1,174.5 (1,049.0-1,315.3)	593.9 (527.7-668.3)
						3-8y	31	1,640.5 (1,094.7-2,458.3)	374.7 (246.7-569.1)
2-4 years post-vaccination									
6	Romanowski, Hum Vacc, 2011	RCT	Canada & Germany	F; 9-14y	2vHPV[e]	2m	201	1,170 (931-1,471)	450 (352-575)
						6m	184	2,274 (1,868-2,768)	980 (765-1,255)
7	Puthanakit, JID, 2016 & Huang, JID, 2017	RCT	Multinational	F; 9-14y	2vHPV	6m	462	1,210.2 (1,124.8-1,302.1)	562.8 (516.4-613.4)
						12m	355	1,559.3 (1,431.2-1,699.0)	804.0 (731.8-883.4)
8	Sankaranarayanan, Lancet Oncol, 2016	Post-hoc analysis of RCT	India	F; 10-18y	4vHPV	2m	513	136 (126-147)	101 (93-109)
						6m	278	163 (147-181)	117 (104-132)
9	LaMontagne, Vaccine, 2014	Cross-sectional follow-up study[f]	Uganda	F; 10y	2vHPV	≤3m	113	No significant difference[g]	
						>3m	28		
5-7 years post-vaccination									
10	Safaeian, Canc Prev Res, 2013 & JNCI, 2018	Post-hoc analysis of RCT,	Costa Rica	F; 18-25y	2vHPV	1m	193	379 (335-429)	228 (198-264)
						6m	79	460 (367-576)	270 (221-330)
11	Toh, CID, 2017	Prospective cohort study[h]	Fiji	F; 9-12y	4vHPV	<6m	22	No significant difference[g,i]	
						≥6m	38		

N: Number; HPV: Human Papilloma Virus; GMT: Geometric mean titers; CI: Confidence intervals; RCT: Randomized controlled trial; y: Years; m: Months; Nab: Neutralizing antibodies.

[a] Numbers of participants contributing to the HPV16 and 18 results by interval are shown. Where numbers contributing to HPV16 and 18 results vary, the highest number is shown.

[b] Data from per protocol analyses are shown where multiple analyses were performed.

[c] 90% CIs were shown for this study.

[d] 173 girls/boys in the 6m interval group received 2 doses of 9vHPV. 31 females in the 3-8y interval group received 1 dose of 4vHPV and 1 dose of 9vHPV.

[e] Participants in the 2m vs 6m interval groups were given an alternative 2vHPV vaccine formulation containing 40 µg of each antigen.

[f] Extended 2-dose interval data are from a post-hoc analysis.

[g] Titers were not presented in the publication.

[h] Analyses of data extracted for this table were retrospective.

[i] Results for this study are neutralizing antibody titers.

Table 2: Observational studies comparing efficacy/effectiveness outcomes with differing intervals between 2 doses of HPV vaccine.

#	Reference(s)	Study design	Location	Gender; age	Vaccine	Outcome measure	Results by interval between dose 1 and 2[a]		
							Interval	N	Estimate (95%CI)
HPV16/18 infection									
1	Safaeian, JNCI, 2018	Post-hoc analysis of RCT	Costa Rica	F; 18-25y at vaccination	2vHPV	Cumulative incident infection over 7y	1m 6m	192 78	3.6 (1.6-7.1) 3.8 (1.0-10.1)
2	Sankaranarayanan, Lancet Oncol, 2016 & Vaccine, 2018	Post-hoc analysis of RCT	India	F; 10-18y at vaccination	4vHPV	Cumulative incident infection over 7y	2m 6m	1,473 1,179	2.2 (1.2-3.2) 0.9 (0.2-1.6)
Cervical abnormalities									
3	Brotherton, Pap Res, 2015	Data-linkage cohort study	Australia	F; ≤26y	4vHPV	Adjusted hazard ratio for CIN3/AIS[b,c]:	<6m ≥6m	20,297 7,204	0.58 (0.26-1.29) 1.97 (0.74-5.26)
4	Dehlendorff, Vaccine, 2018	Population-based registry cohort study	Denmark & Sweden	F; 13-30y	4vHPV	Incidence of CIN2+ per 100,000 pyar	<5m, ≤16y ≥5m <5m, 17-19y ≥5m <5m, 20-29y ≥5m	310,758 28,022 66,320 4,251 136,429 11,748	10.11 (5.99-15.98) 6.23 (1.29-18.22) 94.72 (67.03-130.01) 162.14 (83.78-283.22) 1,122.67 (1,034.92-1,215.89) 1,425.33 (1,123.00-1,784.02)
5	Hofstetter, JAMA Paed, 2016	Retrospective registry cohort study	USA	F; 11-20y	4vHPV	Risk of abnormal cytology	Any ≥6m	376 228	Similar risk reported but stratified results not available
Genital/anogenital warts									
6	Blomberg, CID, 2015	Population-based registry cohort study	Denmark	F; 13-30y	4vHPV	Incidence rate ratio	2m 3m 4m 5m 6m	Data not available	1.0 (ref) 0.73 (0.55-0.96) 0.55 (0.38-0.80) 0.45 (0.31-0.65) 0.37 (0.25-0.56)
7	Hariri, Am J Epidemiol, 2018	Retrospective database cohort study	USA	F; 15-22y	4vHPV	Incidence per 100,000 pyar[d]	<6m ≥6m	2,730 2,729	544.6 (343.1-864.4)) 177.9 (101.0-313.2)
8	Perkins, Sex Transm Dis, 2017	Prospective database cohort study	USA	F; 9-18y	4vHPV	Incidence per 1,000 pyar[d]	<5m ≥5m	18,757 17,826	1.71 (1.46-2.01) 1.84 (1.54-2.20)
9	Zeybek, J Low Genit Tract Dis, 2018	Retrospective database cohort study	USA	M / F; 9-26y	4vHPV	Adjusted hazard ratio relative[c]	<6m, 15-19y ≥6m <6m, ≥20y ≥6m	14,597 13,287 6,955 3,703	0.65 (0.45-0.94) 0.69 (0.44-1.07) 1.11 (0.79-1.55) 1.23 (0.76-1.98)
10	Lamb, BMJ Open, 2017	Population-based registry cohort study	Sweden	F; <20y at vaccination	4vHPV	Incidence per 100,000 pyar	0-3m, ≤16y 4-7m ≥8m 0-3m, 17-19y 4-7m ≥8m	204,103 8,095 1,894 46,712 2,965 615	84 (66-108) 95 (48-190) 351 (168-737) 408 (335-498) 154 (69-344) 603 (271-1343)

[a] Age-standardized or stratified values are shown where provided.
[b] Data shown for participants vaccinated before screening commencement and with 24m censoring time.
[c] Relative to no vaccination.
[d] Data shown for 12m censoring time.